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Polycyclic Aromatic Hydrocarbons and Related Compounds

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20. 3173/2:

HUMAN EXPOSURE, DISTRIBUTION AND EPIDEMIOLOGY STUDIES

1. SKIN CANCER IN PATIENTS WITH PSORIASIS TREATED WITH COAL TAR.

Pittelkow MR, Perry HO, Muller SA, Maughan WZ, O'Brien PC
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Arch Dermatol; 117(8):465-468 1981

For many yr, crude coal tar has been used for the treatment of psoriasis. The po ssible carcinogenic effect of crude coal tar and UV radiation (Goeckerman regimen), considered individually or in combination, has been of some concern to physicians. A 25 yr follow-up study was completed on 280 patients with psoriasis who were hospitalized and treated with crude coal tar and UV radiation at the Mayo Clinic, Rochester, Minnesota during the yr 1950 through 1954. The results of this study suggest that the incidence of skin cancer is not appreciably increased above the expected incidence for the general population when patients are treated with coal tar ointments. It seems that the Goeckerman regimen (topical crude coal tar combined with UV radiation) can be used with minimal risk for skin cancer in the treatment of psoriasis. (Author abstract) (22 Refs)

2. MUTAGENICITY OF URINE FROM PSORIATIC PATIENTS UNDERGOING TREATMENT WITH COAL TAR AND ULTRAVIOLET LIGHT.

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J Invest Dermatol; 77(2):181-185 1981

The possible percutaneous absorption of mutagens from patients receiving crude coal tar (CCT) and UV light was investigated. Urine samples were collected from nonsmoking volunteers, smoking, and nonsmoking psoriatic patients. Patients were treated with 1% CCT USP or 1 to 10% CCT in petrolatum in the evening. The following morning, patients received coal tar baths and then UV light (mainly 290-320 nm, UVB). Nonpolar organics in urine samples were extracted by adsorption onto XAD-2 resin and the extracted organics assayed in the Ames Salmonella/Microsome test. TA98 was the most sensitive bacterial strain to detect mutagenicity. Except for smoking psoriatic patients, the addition of liver homogenate was necessary to see mutagenicity. No increase in the number of revertants was observed when B-glucuronidase was added to the assay. Of 14 patients studied 12 had at least one mutagenic urine sample. Typical values for nonsmoking psoriatics treated with CCT ranged from 42 to 496 his +/20 ml of urine after the subtraction of spontaneous his + counts (26 +-6). Two nonsmoking normal volunteers were found to excrete mutagenic urines. Smoking psoriatic patients ranged from 213 to 1,100 his +/20 ml urine. This study demonstrates the percutaneous absorption of mutagens from CCT and indicates that its effects may not be limited to the skin. (Author abstract) (24 Refs)

UPTAKE AND METABOLISM

3. GLUCURONIC ACID CONJUGATES OF METABOLITES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE EXCRETED THROUGH BILE DUCTS IN RAT.

Khanduja KL, Dogra SC, Sharma RR
Dept. Biophysics, Postgraduate Inst. Medical Education and Res., Chandigarh 160 012, India

Indian J Exp Biol; 19(4):375-378 1981

The nature of metabolites of 7,12-dimethylbenz(a)anthracene (DMBA) excreted thro ugh the biliary ducts of female Wistar rats was examined through thin layer and column chromatography. The results indicated that diols or dihydrodiols and not phenols of DMBA could be the main metabolites which conjugate with glucuronic acid for rapid excretion of the carcinogen in the bile. (24 Refs)

4. METABOLIC STUDY OF 7-METHYLBENZO[A]PYRENE WITH RAT LIVER MICROSOMES: SEPARATION BY REVERSED-PHASE AND NORMAL-PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY AND CHARACTERIZATION OF METABOLITES.

Wong TK, Chiu PL, Yang SK
Dept. Pharmacology, Sch. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014

Chem Biol Interact; 36(2):153-166 1981

The 7-methylbenzo[a]pyrene (7-MBaP) was incubated with liver microsomes of rats pretreated with polychlorinated biphenyls (Aroclor 1254) (PCBs). Metabolites of 7-MBaP were isolated by both reversed-phase and normal-phase high performance liquid chromatography (HPLC) and were characterized by nuclear magnetic resonance, UV-visible and mass spectral analyses. The predominant metabolite of 7-MBaP was found to be 3-hydroxy-7-methylbenzo[a]pyrene (3-hydroxy-7-MBaP). Other identified metabolites include 7-MBaP 4,5-, 7,8- and 9,10-trans-dihydrodiols, 7-hydroxymethyl-BaP, 7-hydroxymethyl-BaP trans-9,10-dihydrodiol, 9-hydroxy-7-MBaP 3-hydroxy-7-hydroxymethyl-BaP, 7-MBaP 1,6-and 3,6-quinones and a hydroxyquinone which is also formed by further metabolism of the 3-hydroxy-7-MBaP. Comparative metabolic studies of 7-MBaP and BaP indicated that, relative to that of BaP, the methyl substituent of 7-MBaP slightly increases the formation of 3-hydroxy-7-MBaP and decreases the metabolism at other regions of the 7-MBaP molecule. The finding that a 7,8-dihydrodiol is a metabolite indicates that, like BaP, 7-MBaP may also be activated to the potentially reactive 7,8-dihydrodiol 9,10-epoxides although their formations are significantly reduced. (Author abstract) (22 Refs)

5. METABOLIC CONVERSION OF DIBENZ[A,H]ANTHRACENE (+-)TRANS-1,2-DIHYDRODIOL AND CHRYSENE(+-)TRANS-3,4-DIHYDRODIOL TO VICINAL DIHYDRODIOL EPOXIDES.

Chou MW, Fu PP, Yang SK
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Proc Natl Acad Sci USA; 78(7,part2):4270-4273 1981

The hydroxyl groups of dibenz[a,h]anthracene trans-1,2-dihydrodiol and chrysene trans-3,4-dihydrodiol are known to be predominantly in quasi-axial conformations. These dihydrodiols were metabolized by liver microsomes from 3-methylcholanth-

rene-pretreated rats to form 1,2,3,4-tetrahydrotetrols as the major products. The major metabolites of the dihydrodiols were isolated by reversed-phase high-performance liquid chromatography and identified by UV-visible absorption and mass spectral analyses. The results indicate that axial hydroxyl groups of dibenz[a,h]anthracene trans-1,2-dihydrodiol and of chry sene trans-3,4-dihydrodiol do not direct metabolism away from their respective vicinal double bond. (Author abstract) (27 Refs)

6. INTERACTION BETWEEN BENZO[ALPHA]PYRENE AND MOUSE SKIN IN ORGAN CULTURE.

Smith LH, Holland JM
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Toxicology; 21(1):47-57 1981

Discs of skin from male and female C3Hf/HeBd mice were incubated on Tyrode soln with 10 milliM NaHCO3, or on synthetic or fetal calf serum media. Tritiated benzo-alpha-pyrene (BP) (0.5 uCi) in acetone was placed on each disc. The appearance of radioactivity in polar and nonpolar phases of the medium was measured. Most portions of the skin remained intact for the first 48 hr. After that necrosis began to develop, becoming extensive by day 6. Radioactivity in the medium accumulated at the rate of 1.5%/hr up to 24 hr, and at the rate of 0.4%/hr up to 48 hr. After 48 hr about 45% of the radioactivity was in the medium. For female skin the figure was about 33% higher than for male skin. Nonphysiologic conditions inhibited the appearance of radioactivity in the medium. Appearance rates varied with temperature, being 0.06%, 0.12%, and 1.5% for 0, 24, and 37 C, respectively. Use of benzene, ethyl acetate, cyclohexane/acetone, or methanol as the vehicle for applying BP, in place of acetone, did not affect the results. With 100% fetal calf medium, the accumulation of radioactivity was increased (46% at 24 hr and 59% at 48 hr). Little variation was noted using different vol of medium or vehicle. Most of the radioactivity present in the medium was polar in nature. Evidently the appearance of BP in the medium required metabolic processes. Further research in to interactions between mammalian skin and hydrocarbons is recommended. (21 Refs)

7. DOSE-DEPENDENT INDUCTION OF RAT LIVER MICROSOMAL ARYL HYDROCARBON MONOOXYGENASE BY BENZO[K]FLUORANTHENE.

Schmoldt A, Jacob J, Grimmer G
(c/o Jacob), Biochemisches Institut fur Umweltcarcinogene, Sieker Landstrasse 19, D-2070 Ahrensburg, W. Germany
Cancer Lett; 13(3):249-257 1981

The ability of benzo(k)fluoranthene (BFK) to act as an inducer was demonstrated by recording the benz(a)anthracene metabolite profile in rat liver by means of the gas chromatography/mass spectrometry (GC/MS) technique. Male Wistar rats (120-150 g body wt) were pretreated ip with doses of 0.01 up to 100 mg/kg/day x 3. Liver microsomes were then prepared and the protein as well as the cytochrome P-450 concentrations were determined. The dose response curve for BKF indicated that max response was obtained at 3 x 10 mg/kg of BFK. The 50% effective dose was estimated to be about 3 x 0.6 mg/kg body wt. Separation of the benz(a)anthracene metabolites indicated that in contrast to benz(a)pyrene almost no phenols were formed and dihydrodiols and dihydrodiol epoxides were the main metabolites. The formation o f the 8,9-as well as the 5,6-dihydrodiol was stimulated to about the same extent whereas the 10,11-dihydrodiol was suppressed. Among benz(a)anthracene metabolites from liver microsomes of BFK pretreated rats was one which corresponds in all parameters with the postulated ultimate carcinogen 3,4-dihydroxy-1,2-epoxy-1,2,3,4 tetrahydrobenz(a)anthracene. This metabolite and some other primary and secondary oxidation products could be identified after incubation with induced, but not with normal microsomes. (23 Refs)

BINDING TO CELLULAR MACROMOLECULES

8. DNA MODIFICATION IN RAT LUNGS FOLLOWING INTRATRACHEAL OR SUBCUTANEOUS ADMINISTRATION OF 4-NITROQUINOLINE-1-OXIDE, BENZO[A]PYRENE OR 2-AMINOANTHRACENE.

Harpaz R, Mitchell C
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87115
Chem Biol Interact; 36(2):129-140 1981

Benzo[a]pyrene (BP)-,2-aminoanthracene (2AA)- and 4-nitroquinoline-1-oxide (4NQO)-mediated DNA modification were investigated in rat lungs by using alkaline sucrose gradient sedimentation. The exposure-route, the physicochemical nature of the administered compound and the number of treatments were all important in determining the extent of DNA modification. 4NQO produced qualitatively similar modification whether instilled intratracheally (it) as a suspension or injected sc in a soluble form. BP and 2AA produced no DNA alteration when injected sc; they did, however, modify DNA sedimentation when instilled as a suspension, but not until 24 hr after treatment. Furthermore, BP caused no DNA modification at any sampling time when instilled in a lipid solvent. In contrast to the DNA modification observed at 24 hr after a single it treatment with a BP suspension, no such alteration was detected 12 or 24 hr after the last of five similar daily treatments. These results are discussed with respect to mechanisms of differential transport, clearance and metabolism of administered carcinogens. (Author abstract) (36 Refs)

METABOLIZING ENZYME SYSTEMS FOR POLYCYCLIC AROMATIC HYDROCARBONS

9. ARYL HYDROCARBON HYDROXYLASE ACTIVITY IN RAT MAMMARY FIBROBLASTS GROWN IN PRIMARY CULTURE.

Greiner JW
Lab. Biology, NIH, NCI, Building 37, Room 2A19, Bethesda, MD, 20205
Biochem Pharmacol; 30(13):1873-1876 1981

The induction of aryl hydrocarbon hydroxylase (AHH) in rat mammary fibroblast by 7,12-dimethylbenz(a)anthracene and other carcinogenic polycyclic aromatic hydrocarbons is reported. The fibroblast AHH activity differed significantly from that previously observed in mammary epithelial cells. (20 Refs)

10. ENZYMIC HYDROXYLATION OF BENZO(A)PYRENE AT THE 6-POSITION BY VITAMIN K1-HYDROPEROXIDE AND RAT LUNG HYDROPEROXIDASE.

Sloane N

Dept. Biochemistry, Univ. Tennessee, Center for Health Sci., Coll. Medicine, Mem phis, TN, 38163

Xenobiotica; 11(4):267-274 1981

The role of vitamin K1 in the hydroxylation of benzo(a)pyrene (BP) at the 6-position is correlated with the oxidative formation of vitamin K1-hydroperoxide and its subsequent reaction with BP in the presence of soluble rat lung hydroperoxidase. Vitamin K1-hydroperoxide was synthesized from vitamin K1 and its structure verified by mass spectral analysis and enzymic studies. The major product (the 3,6-BP dione) that results from the non-enzymic oxidation of 6-hydroxy-BP was isolated from the enzymic reaction and characterized by spectroscopic studies. Thiodione (the menadione-glutathione adduct) inhibits both aryl hydrocarbon hydroxylase activity and vitamin K1-hydroperoxide/hydroperoxidase activity. (Author abstract) (31 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS INDUCED BY POLYCYCLIC AROMATIC HYDROCARBONS

11. INDUCTION OF ALDEHYDE DEHYDROGENASE BY POLYCYCLIC AROMATIC HYDROCARBONS IN RATS.

Torronen R, Nousiainen U, Hanninen O

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Chem Biol Interact; 36(1):33-44 1981

Short-term intragastric administration of selected polycyclic aromatic hydrocarbons (100 mg/kg daily for 4 days) to male Wistar rats resulted in marked changes in liver cytosolic aldehyde dehydrogenase activity. Non-carcinogenic anthracene, phenanthrene and chrysene produced a 2.5-3-fold increase in the activity assayed with propionaldehyde as substrate and NAD as coenzyme. Weakly carcinogenic 1,2-benzanthracene enhanced aldehyde dehydrogenase activity 9-fold and the potent carcinogens 3,4-benzpyrene and 3-methylcholanthrene 30-fold. With benzaldehyde as substrate and NADP as coenzyme the differences between the groups were even more pronounced. Somewhat similar but less manifest effects on aldehyde dehydrogenase activity were detected also in the liver microsomes and in the postmitochondrial fractions of the small intestinal mucosa. On the basis of their ability to induce aldehyde dehydrogenase activity the compounds could be divided into three groups. This classification was found to correlate well with the carcinogenic potency of the compounds. It appeared that the exposure to polycyclic aromatic hydrocarbons, especially the carcinogenic ones, was followed by synthesis of a new aldehyde dehydrogenase form. This, new form was differentiated from the normally existing cytosolic aldehyde dehydrogenase by its ability to oxidize benzaldehyde in the presence of NADP. (Author abstract) (15 Refs)

12. ON THE URIDINEDIPHOSPHATE (UDP) KINASE OF 9,10-DIMETHYL-1,2-BENZANTHRACENE (DMBA)-INDUCED TONGUE CANCER.

Ohsaka F, Okada Y, Asanami S, Kizaki H, Sakurada T

Dept. Dentistry, Sch. Medicine, Keio Univ., Shinjuku-ku, Tokyo 160, Japan

Nippon Kokuka Gakkai Zasshi; 30(1):96-102 1981

Tongue cancer was induced with 9,10-dimethyl-1,2-benzanthracene (DMBA) in male golden hamsters that were 4 wk old at the beginning of the experiment. The hamsters were pathohistologically confirmed to have squamous cell carcinoma. The liver, tongue and tongue cancer from which the blood and necrotized parts were carefully removed and the tongue tissue from which the muscular layer was carefully removed were homogenized. The homogenate was centrifuged at 100,000 x g for 60 min, and the supernatant was used as the enzyme preparation. The [14C]uridine triphosphate produced from [14C]uridine diphosphate (UDP) was separated and its radioactivity was used as the indication of uridine diphosphate kinase activity. The UDP kinase of normal tongue mucosal tissue and tongue cancer tissue had an optimum pH at 7.5 but that of the normal liver had two peaks, one at pH 6.5 and the other at pH 8.0. The activity of UDP kinase in the different organs was saturated at about 2.5 mM UDP. The substrate affinity (apparent Km) was 0.6 mM, 0.8 mM and 0.8 mM for the normal tongue mucosal tissue, tongue cancer tissue and normal hepatic tissue, respectively. The UDP kinase activity of the different organs was saturated at about 10 mM ATP-Mg2+ and the substrate affinity (apparent Km) was 2.5 mM for all the organs. The UDP kinase activity of normal tongue mucosal tissue and that of normal liver tissue were almost the same, but that of the tongue cancer tissue was about 1.3x higher than that of the normal tongue mucosal tissue. However, that of the mucosal tissue of tumor-bearing tongues was not increased. The highest activity peak of UDP kinase from tongue mucosal tissue was obtained at an isoelectric focusing point of pH 8.5 and that of the hepatic tissue of PH 6.9. The electrophoretic pattern of tongue cancer tissue was similar to that of normal tongue mucosal tissue, but the peak at pH 7.14 obtained with tongue mucosal tissue was not clear. (13 Refs) (In JPN)

13. ADMINISTRATION OF 3-METHYLCHOLANTHRENE TO RATS INCREASES THE SPECIFIC HYBRIDIZABLE MRNA CODING FOR CYTOCHROME P-450C.

Bresnick E, Brosseau M, Levin W, Reik L, Ryan DE, Thomas PE

Dept. Biochemistry, Univ. Vermont Coll. Medicine, Burlington, VT, 05405

Proc Natl Acad Sci USA; 78(7,part2):4083-4087 1981

Poly(A)+-RNA obtained from the livers of 3-methylcholanthrene (3MC)-treated rats was translated into cytochrome P-450c in a cell-free reticulocyte system. In this translational system, no precursor cytochrome P-450c was observed. The mRNA responsible for the synthesis of this cytochrome was isolated by immunoprecipitation of liver polyribosomes obtained at 15 hr after 3MC treatment, and a cDNA was constructed by the reverse transcriptase reaction. The cDNA was further purified by hybridizing at a high Rot (product of RNA concentration and incubation time) to poly(A)+-RNA isolated from control rat liver, and the nonhybridized, single-stranded cDNA was isolated by hydroxylapatite chromatography. This cDNA(P-450c)was employed in hybridization reactions with poly(A)+-RNA isolated from the livers of rats treated with 3MC for various times. These studies indicated a maximal induction of mRNA(P-450c) at about 15 hr after 3MC injection, although levels of this mRNA were significantly increased by

7 hr. The mRNA(P-450c) concentration had diminished by 24 hr but remained higher than control levels for at least 48 hr. These studies establish an effect of 3MC upon the accumulation of mRNA(P-450c) in rat liver. (Author abstract) (41 Refs)

FACTORS MODIFYING THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

14. INITIATION AND PROMOTION AT DIFFERENT AGES AND DOSES IN 2200 MICE. I. METHODS, AND THE APPARENT PERSISTENCE OF INITIATED CELLS.

Stenback F, Peto R, Shubik P
Dept. Pathology, Univ. Oulu, SF 90220, Oulu 22, Finland
Br J Cancer; 44(1):1-14 1981

Delay between initiation and promotion on mouse skin was in 1949 reported by Berenblum and Shubik not to affect tumor yields, and this led to the important concept of the irreversibility of initiation and stimulated the development of multistage models. Subsequent reports have, however, suggested that delay does decrease tumor yields, and this is confirmed by the present study of 2,200 mice initiated at 8, 48, or 68 wk with 10, 30, 100, or 300 ug of DMBA and promoted by a standard dose of TPA for 15 wk, after various delays. However, our data suggest that the decrease in tumor yields is chiefly or wholly due to a reduction, among ageing mice, of the ability to respond to promoters, and not to any substantial loss of initiated cells, for late initiation with immediate promotion also yielded a less rapid response than early initiation with immediate promotion. Interpretation of all such studies is complicated by the few wk that the skin needs to repair ulceration and other damage induced by the higher doses of DMBA, for if promotion with TPA begins before such repair is complete the tumor yield may be misleadingly increased. (Author abstract) (25 Refs)

15. INITIATION AND PROMOTION AT DIFFERENT AGES AND DOSES IN 2200 MICE. III. LINEAR EXTRAPOLATION FROM HIGH DOSES MAY UNDERESTIMATE LOW-DOSE TUMOUR RISKS.

Stenback F, Peto R, Shubik P
Dept. Pathology, Univ. Oulu, SF 90220, Oulu 22, Finland
Br J Cancer; 44(1):24-34 1981

The dose-response relationships from the data described in Paper I were analyzed. Among unpromoted animals, only doses sufficient to cause ulceration with subsequent promotion due to wound healing caused a rapid crop of tumors, so the dose-response curve exhibited strong upward curvature. Among promoted animals, the response of the skin to initiation appeared to have been nearly saturated by all dimethyl benzanthracene (DMBA) doses tested, so that a 30-fold decrease in dose produced only a 3-fold decrease in effect. The dose-response relationship thus exhibited strong downward curvature. Among promoted animals, estimation of the risks associated with very low doses of carcinogen by linear extrapolation through the origin from the effects of larger doses (which is often assumed to be conservative) would underestimate the true risks by 10-fold or more. Our results emphasize that whereas linear interpolation from the results of high doses may be reasonable for data on the effects of continuous treatment with non-toxic dose levels of carcinogen, it may be misleading when extrapolating, as here, from the effects of single large doses. (Author abstract) (18 Refs)

16. THE NATURE OF THE EPIDERMAL GROWTH PRODUCED BY THE FIRST APPLICATION OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON THE SKIN OF MICE INITIATED WITH DIMETHYLBENZANTHRACENE.

Argyris TS
Dept. Pathology, State Univ. New York, Upstate Medical Center, Syracuse, NY, 13210
J Invest Dermatol; 77(2):230-234 1981

We have investigated the kinetics of epidermal growth following a single application of 17 nmoles of 12-O-tetradecanoylphorbol-13-acetate (TPA) in the back skin of CD-1 female mice initiated with 200 nmoles of dimethylbenzanthracene (DMBA). Within 5 hr after the application of TPA there is an increase in epidermal wet wt and total protein (protein/unit area of epidermis) which reached their peak of 3 to 4x that of normal between 3 and 4 days. Total DNA reaches its peak of about 2x increase above normal by day 2. All these parameters remain elevated until 7 days after TPA treatment when they begin to return toward normal levels. But, by day 10, the end of the experimental period, they are still significantly elevated above normal levels. The principal hyperplasia appears with marked increases in the number of nucleated cell layers, the total number of nuclei/mm interfollicular epidermis (IFE) and the number of suprabasal nuclei/mm IFE which by day 2 reach their peak of about 2-3x normal; one sees considerable epidermal cell damage as evidenced by cytoplasmic vacuolization, nuclear pyknosis, and the separation of the epidermis from the dermis. This period of damage is associated with a decrease in the number of basal nuclei/mm IFE. A comparison of the epidermal growth produced by the first application of TPA in initiated mouse skin with that in normal mouse skin, suggests that the overall growth produced by the first application of TPA in initiated mouse skin is of greater duration than that produced by TPA in normal mouse skin. (24 Refs)

17. EFFECTS OF RETINOIDS ON NEOPLASTIC TRANSFORMATION, CELL ADHESION, AND MEMBRANE TOPOGRAPHY OF CULTURED 10T1/2 CELLS.

Bertram JS, Mordan LJ, Blair SJ, Hui S
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263
Ann NY Acad Sci; 359:218-236 1981

The effects of retinoids on cell biology was studied in readily transformable C3H/10T1/2 CL8 cell line of mouse embryo fibroblasts. Included are studies on membranes and membrane interactions (cell/substrate adhesion, cell spreading, surface topography). Retinyl acetate caused a dose-dependent reversible inhibition of neoplastic transformation induced by 3-methylcholanthrene. Similar effect was recorded for retinol and retinaldehyde, while all-trans- and 13-cis-retinoic acids failed to inhibit transformation of 10T1/2 cells. Retinoids had no effect on the growth of established cells after the phenotypic expression of transformation. Analysis of the effect of retinoids on cell/substrate adhesion showed that retinyl acetate induced a dose-dependent decrease in the rate of release of trypsin-treated cells. The synthetic retinoids showed an extremely variable response in the adhesion assay. Retinyl acetate at 0.5 ug/ml increased the cell spreading as evidenced by a threefold increase in upper cell surface area and a pronounced increase in the percent of flattened cells. (29 Refs)

18. EFFECT OF VITAMIN A (VA) ON SKIN CANCER INDUCTION BY 20-METHYLCHOLANTHRENE (20-MC) IN MICE (MEETING ABSTRACT).

Hirose R, Hori M, Yamashiro K, Yoshida H
Dept. Dermatology, Nagasaki Univ., Sch. Medicine, Sakamoto-cho, Nagasaki 852, Japan

Nippon Hifuka Gakkai Zasshi; 91(3):257 1981

One hundred twenty d-d strain mice (3 wk old) were divided into three groups as follows: group 1 (30 mice), administration of 20-methylcholanthrene (20-MC) alone; group 2 (30), combined administration of croton oil and 20-MC; and group 3 (60), combined administration of vitamin A (VA) and 20-MC. The incidence and process of carcinogenicity in each group were examined by light and electron microscopy. Carcinogenicity was markedly inhibited in group 3 compared with groups 1 and 2. Tonofilaments of tumor cells and a decrease in desmosomes were observed in group 3. (no Refs) (In JPN)

19. THE INFLUENCE OF RETINOIDS ON POLYAMINE AND DNA SYNTHESIS IN MOUSE EPIDERMIS.

Boutwell RK, Verma AK
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706

Ann NY Acad Sci; 359:275-280 1981

The effect of retinoic acid (RA) on skin carcinogenesis in mice was studied. RA did not affect the yield of skin papillomas induced by repeated applications of dimethylbenzanthracene (DMBA). RA application in initiation-promotion protocol (single DMBA application at a dose that does not produce tumors followed by repeated applications of the promoter 12-O-tetradecanoylphorbol-13-acetate: TPA) inhibited the yield of skin papillomas. RA did not inhibit the induction in epidermis of ornithine decarboxylase (ODC) by DMBA, but reduced markedly induction of ODC by TPA. RA pretreatment enhanced initial depre ssion of DNA synthesis in mouse skin by TPA. RA pretreatment did not change DNA synthesis following a carcinogenic dose of DMBA. (24 Refs)

20. SKIN TUMOR-PROMOTING ACTIVITY OF BENZOYL PEROXIDE, A WIDELY USED FREE RADICAL-GENERATING COMPOUND.

Slaga TJ, Klein-Szanto AJ, Triplett LL, Yotti LP, Trosko JE
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Science; 213(4511):1023-1025 1981

Benzoyl peroxide, a widely used free radical-generating compound, promoted both papillomas and carcinomas when it was topically applied to mice after 7,12-dimethylbenz[a]anthracene initiation. Benzoyl peroxide was inactive on the skin as a complete carcinogen or as a tumor initiator. A single topical application of benzoyl peroxide produced a marked epidermal hyperplasia and induced a large number of dark basal keratinocytes, effects similar to those produced by the potent tumor promoter 12-O-tetradecanoyl phorbol-13-acetate. Benzoyl peroxide, like other known tumor promoters, also inhibited metabolic cooperation (intercellular communication) in Chinese hamster cells. In view of these results caution should be recommended in the use of this and other free radical-generating compounds. (Author abstract) (24 Refs)

21. MODIFICATION OF LUNG TUMOR DEVELOPMENT IN A/J MICE.

Witschi HP, Hakkinen PJ, Kehrer JP
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Toxicology; 21(1):37-45 1981

Male and female A/J mice (age 6-8 wk) were divided into five groups with controls. The first group received 500 mg/kg urethan ip. One wk later weekly injections of 300 mg/kg butylated hydroxytoluene (BHT), 500, 300, or 150 mg/kg butylated hydroxyanisole (BHA), or 1,000 mg/kg vitamin E began. The second group received either 10 mg/kg 3-methylcholanthrene (3-MC), 2 injections 1 wk apart, or 7 mg/kg dimethylnitrosamine (DMN), given once. After 1 wk 4 weekly injections of 300 mg/kg BHT were begun. The third group received 500 mg/kg urethan ip, followed after 1 wk by 80 mg/kg methylcyclopentadienyl manganese tricarbonyl (MMT). The fourth group received 400 mg/kg BHT, followed immediately by either a single injection of urethan or a continuous exposure to urethan. The last group received 400 mg/kg BHT followed after 2 wk by either 1,000 or 500 mg/kg urethan. The results show that BHT enhances the development of tumors induced by urethan, 3-MC, or DMN. BHA and vitamin E did not have this effect. MMT produced cell proliferation, but did not enhance carcinogenesis. Apparently the antioxidant property of BHT was not related to effect on tumor development. Rapidly dividing lung cells were not more susceptible to tumor development than resting lung cells. (21 Refs)

22. EFFECT OF GLUTATHIONE AND URIDINE 5'-DIPHOSPHOGLUCURONIC ACID ON MUTAGENESIS BY BENZO[A]PYRENE AND AFLATOXIN B1 IN THE SALMONELLA/MICROSOME ASSAY.

Malaveille C, Brun G, Hautefeuille A, Bartsch H
Programme of Environmental Carcinogens and Host Factors, Div. Chemical and Biological Carcinogenesis, International Agency for Res. on Cancer, 150 cours Albert-Thomas, F-69372 Lyon Cedex 2, France

Mutat Res; 83(1):15-24 1981

The role of the conjugating enzymes, glutathione-S-transferase (GSH-S-T) and uridine 5'-diphosphoglucuronic acid (UDPGA) on rat liver S9-mediated mutagenesis of benzo(a)pyrene (BP) and aflatoxin B1 (AFB) in the Salmonella/microsome assay was investigated. In S typhimurium TA100, the UDPGA-dependent reduction of BP mutagenicity was related to the liver S9 concentration: max reduction (40%) in mutagenicity was noted with an S9 concentration of 50 ul/plate. In liquid assays, the presence of 2.5 milliM UDPGA for 20 min caused a two-fold increase in BP mutagenicity at a concentration of 40 uM BP. At 20 uM BP, the presence of UDPGA either did not change or decreased mutagenicity of BP; after 30 min of incubation, a significant decrease was observed. With 20 and 40 uM BP, the addition of GSH to the assays decreased BP mutagenesis by 1.8-and 1.5-fold in the presence of 17% and 9% (vol/vol) liver S9, respectively. GSH had no effect at two-fold lower concentrations of BP. The effect of glutathione (GSH) on AFB mutagenesis was dependent on its concentration. AFB mutagenicity decreased at concentrations of AFB greater than 7.5 nanoM; at 30 nanoM AFB, the AFB mutagenesis was reduced by 1.8-fold. In liquid assays, in the presence of 4.4% S9 from untreated rats the addition of 10 milliM GSH changed the AFB mutagenesis only at concentrations greater than 100 nanoM, resulting in an enhancement of AFB mutagenicity. (43 Refs)

23. RELATIONSHIP OF HORMONES TO INHIBITION OF MAMMARY TUMOR DEVELOPMENT OF UNDERFEEDING DURING THE 'CRITICAL PERIOD' AFTER CARCINOGEN ADMINISTRATION (MEETING ABSTRACT).

Sylvester PW, Aylsworth CF, Van Vugt DA, Meites J
Physiology Department, Neuroendocrine Research Laboratory, Michigan State University, East Lansing, MI, 48824
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Seven days prior to 7,12-dimethyl-benz(a)anthracene (DMBA) administration, virgin 50-day old female Sprague-Dawley rats were placed on a food-restricted diet and continued on this regimen until 30 days after DMBA injection. One day prior to and seven days after DMBA administration, animals were given daily 0.1 ml sc injections of 0.9% NaCl (controls), haloperidol (HAL, 0.5 mg/kg) to increase prolactin (PRL) secretion, growth hormone (GH, 0.5 mg/kg), estradiol benzoate (EB, 1 ug/rat), or a combination of HAL, EB and GH. Drug and hormone treatments were terminated after 8 days, but underfeeding continued for 30 days after DMBA administration after which time all animals were placed on ad libitum feeding fo r the remainder of the 26 wk experiment. Food restriction for 7 days prior to and 30 days after DMBA administration resulted in a significant reduction in av tumor number and size by the end of the 26 wk experiment. Treatment for 8 days with EB produced a significant increase in mammary tumor incidence despite underfeeding, whereas underfed rats given the combination of HAL, EB and GH showed development and growth of mammary tumors equal to that of full-fed controls. Both EB and HAL significantly raised blood PRL levels. GH alone had no apparent effect on mammary tumor incidence. These results indicate that reduced food intake during the 'critical period' for induction of mammary tumor development throughout the 6 mo period of this experiment, and that administration of EB or the combination of EB, HAL and GH for only 8 days can counteract the inhibition by underfeeding. (no Refs)

24. ABORTION VERSUS PARITY: ENDOCRINOLOGICAL FINDINGS IN RELATION TO RAT MAMMARY GLAND CARCINOGENESIS (MEETING ABSTRACT).

Ciocca DR, Russo J
Experimental Pathology Laboratory, Michigan Cancer Foundation, Detroit, MI, 48201
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

The incidence of 7,12-dimethylbenz(a)anthracene (DMBA) - induced rat mammary carcinogenesis is higher in young virgin (V) rats and in rats undergoing pregnancy interruption (PI) than in parous (P) rats. The protective effect of pregnancy on tumor development is attributed to the complete differentiation of the gland attained through pregnancy and lactation and not to differences in serum prolactin (PRL) levels. In order to determine whether the higher susceptibility to carcinogenesis observed in V and PI rats is related or not to serum estradiol levels and the content of prolactin (PRL), luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the pituitary gland, the following study was carried out. V, PI and P rats received 10 mg DMBA/100 g body wt. Ten rats per group were decapitated: 1) at the time of carcinogen administration, 2) 1 wk and 3) 22 wk after DMBA treatment. Serum estradiol levels were determined by radioimmunoassay. Pituitary gland, adrenals and ovaries were processed for light microscopy. The presence of PRL, LH and FSH cells in hypophyses was determined by the PAP method and quantitated with an image analysis system. The results showed that PI rats had higher estradiol levels and more PRL cells than V and P rats at the time of DMBA treatment. One and 22 wk after carcinogen administration, the three groups showed high estradiol in serum and numerous PRL cells but no changes in FSH or LH cells. Seven days post-DMBA treatment neither PI rats nor P rats showed the adrenal necrosis observed in V rats. Twenty-two wk post-DMBA treatment all the groups presented hyperplastic nodules in adrenal cortex and numerous corpora lutea, while some of the PI rats also developed ovarian tumors. These results suggest that the levels of estradiol and the morphological changes in pituitary, adrenals and ovaries are not related to the variations in susceptibility of the mammary gland to carcinogenesis. (1 Ref)

25. EFFECTS OF PROTEIN DIET ON THE DEVELOPMENT OF DMBA-INDUCED MAMMARY TUMORS AND PROLACTIN RELEASE IN FEMALE RATS (MEETING ABSTRACT).

Huang HH, Kissane JQ, Drab E, Hawrylewicz EJ
Department of Research, Mercy Hospital and Medical Center, Chicago, IL, 60616
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Virgin Sprague-Dawley rats were fed ad libitum 8%, 19.5% or 31% isocaloric protein diets for a period of 3 wk before mating. The diets were maintained throughout the mating, gestation and lactation periods. After weaning, all pups were continued on their respective diets and fed ad libitum the entire experimental period. Dimethylbenzanthracene (DMBA) was administered intragastrically at a dose of 5/mg per rat at the age of 7 wk or 3 mg/100 g body wt at the age of 3 wk after vaginal opening. Serum prolactin was measured at the time of DMBA administration and 6 mo after DMBA treatment. The age of sex maturation and estrus cycles also were monitored during the experimental period. Six mo after DMBA exposure, 59% in 8%; 65% in 19.5% and 80% in 31% protein diet rats exhibited palpable mammary tumors when the animals were treated with DMBA at the age of 7 wk. Similarly, DMBA administration at 3 wk after vaginal opening, 12% in 8%; 29% in 19.5% and 49% in 31% protein diet rats showed mammary tumors. Serum prolactin was significantly lower in 8% protein diet animals at the age of 7 wk than any stage of estrus cycle of 19.5% or 31% protein diet animals. Significantly less prolactin was detected in 8% protein diet animals at 3 wk after vaginal opening, as compared to the same stages of estrus cycle of 19.5% or 31% protein diet animals at the same reproductive age. There was no significant difference in prolactin among these 3 groups of animals at 6 mo after DMBA treatment. These results suggest that the lower incidence of DMBA induced mammary tumors in lower protein diet rats may be due to the low prolactin profile at the time of DMBA exposure. (no Refs)

26. RELEASE OF MUTAGENIC METABOLITES OF BENZO[A]PYRENE FROM THE PERFUSED RAT LIVER AFTER INHIBITION OF GLUCURONIDATION AND SULFATION BY SALICYLAMIDE.

Bock KW, Bock-Hennig BS, Lilienblum W, Volp RF
Dept. Pharmacology and Toxicology, Univ. Gottingen, Kreuzbergring 57, D-3400 Gottingen, W. Germany
Chem Biol Interact; 36(2):167-177 1981

The role of glucuronide and sulfate conjugation in presystemic inactivation of b enzo[a]pyrene (BP) metabolites was investigated with rat livers perfused with BP (12 u moles). Comparisons were made between metabolite profiles and mutagenicity of medium from perfusions with and without salicyclamide, a selective inhibitor of glucuronide and sulfate conjugation. After 4 hr perfusion in the presence of salicylamide, certain BP metabolites (diols, quinones, phenols, and metabolites more polar than BP-9,10-diol) were significantly increased at the expense of quinones and phenols in the glucuronide fraction. Mutagenicity of medium (detected by the Ames test, using tester strains TA98 and TA100) was low in perfusion without salicylamide. Mutagenicity detected with tester strain TA98 was significantly increased in perfusions with salicylamide. Involvement of glucuronidation in BP inactivation was also observed at the subcellular level when cofactors of glucuronidation were added to liver homogenates along with the NADPH regenerating system in the Ames test, BP mutagenicity was markedly decreased. Both the activation of BP to mutagenic metabolites and the inactivation of BP metabolites by glucuronidation was much more pronounced with liver homogenates from 3-methyl-cholanthrene-treated rats than with those from phenobarbital-treated animals or untreated controls. The results suggest an important role for glucuronidation and sulfation in the inactivation and elimination of polycyclic aromatic hydrocarbons. (Author abstract) (26 Refs)

TUMORIGENICITY, MUTAGENICITY AND IN VITRO TRANSFORMATION STUDIES

27. EXPERIMENTAL STUDY OF TUMOR INDUCTION BY CHEMICAL CARCINOGENS.

Sanchez Cousteau JA, Justo Alpanes E, Ledro Molina D, Astolfi Perez de Busman J, Ferreiro Madueno M, Ramirez Martinez L, Aguilera Moreno-Aurioles A, Garrido Peralta M
Catedra de Patologia y Clinica Medicas, Hospital Universitario de la Facultad de Medicina, Sevilla, Spain
Rev Clin Esp; 161(2):95-97 1981

Tumor induction was studied in three animal species (Wistar rats, Syrian hamsters and guinea pigs) injected with either methylbenzanthracene or methylcholanthrene in olive oil. Latency of tumor development was 90 +-10 days and was independent of dose and species. Sarcomas were formed in all animals and no metastases were observed. (11 Refs) (In SPA)

28. THE USE OF ADULT RAT LIVER CULTURES IN THE DETECTION OF THE GENOTOXICITY OF VARIOUS POLYCYCLIC AROMATIC HYDROCARBONS.

Tong C, Laspia MF, Telang S, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Environ Mutagen; 3(4):477-487 1981

The application of the hepatocyte primary culture (HPC)-DNA repair test and the adult rat liver epithelial cell (ARL)-hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutagenesis assay to the detection of the genotoxicity of polycyclic aromatic hydrocarbons (PAHs) is described. In the HPC -DNA repair test, dose-dependent increases in DNA repair synthesis were observed in hepatocytes after exposure to carcinogenic PAHs. The noncarcinogenic analogs pyrene, benzo(e)pyrene, chrysene, 1-methylphenanthrene, and anthracene were consistently negative. Benz(a)anthracene was also positive in this assay. In the ARL-HGPRT assay, exposure of clone ARL 18, a stable spontaneous 6-thioguanine-resistant (TGr) ARL mutant, to benzo(a)pyrene resulted in a significant increase in the TGr mutant incidence. Exposure of ARL 18 to another PAH, 7,12-dimethylbenz(a)anthracene also resulted in a significant increase in TGr mutant incidence. The weakly carcinogenic analog benz(a)anthracene, however, was not mutagenic in ARL 18 2 of the 3x it was assayed. The results indicated that the HPC-DNA repair test and the ARL-HGPRT assay, which embody intact cellular metabolism, provide sensitive assays for the detection of inactivation-dependent genotoxic chemicals. (41 Refs)

29. SISTER-CHROMATID EXCHANGE INDUCTION BY POLYCYCLIC AROMATIC HYDROCARBONS IN AN INTACT CELL SYSTEM OF ADULT RAT-LIVER EPITHELIAL CELLS.

Tong C, Brat SV, Williams GM
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Mutat Res; 91(6):467-473 1981

The induction of sister-chromatid exchange (SCE) by several polycyclic aromatic hydrocarbons was studied in the adult rat liver epithelial cell line ARL 18. This line was chosen for its intrinsic capability for metabolic activation of a broad spectrum of mutagens and carcinogens. Cells in the log phase of growth were exposed to various concentrations of carcinogens for 24 hr, then incubated for 48 hr with 12 ug/ml bromodeoxyuridine to facilitate sister-chromatid differentiation. Both benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene induced a significant increase in SCE in ARL 18 over parallel run controls. Both mutagens/carcinogens also produced a log dose-related response. Their noncarcinogenic analogues, benzo[e]pyrene, pyrene, and anthracene did not enhance SCE frequency. The carcinogen benz[a]anthracene was also weakly positive in the ARL/SCE assay. The results confirm the capacity of ARL 18 cells to generate genotoxic metabolites from activation-dependent mutagens/carcinogens and indicate a relationship between the production of mutations and SCEs by polycyclic aromatic hydrocarbons. The assay could be a useful and sensitive addition to a battery of assays in which endpoints differ in their molecular mechanisms. (26 Refs)

30. EVIDENCE THAT BENZO(A)PYRENE-RESISTANT, ARYL HYDROCARBON HYDROXYLASE-DEFICIENT VARIANTS OF MOUSE HEPATOMA LINE, HEPA-1, ARE MUTATIONAL IN ORIGIN.

Hankinson O
Lab. Biomedical and Environmental Sciences, Univ. California, Los Angeles, CA, 90024
Somatic Cell Genet; 7(4):373-388 1981

The ability of treatment with known mutagens to increase the frequency of benzo(a)pyrene resistant (BPr) variants was examined. The phenotypic stability of the variants was studied as a function of time in culture and with respect to the degree of heterogeneity among subclones. The in vitro heat lability of

the aryl hydrocarbon hydroxylase (AHH) was examined. All strains used were derivatives of the subclone Hepa-1c1c7 of the mouse hepatoma line Hepa-1. Four agents with three distinctly different modes of mutagenic action were used: N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate (alkylating agents), ICR-191G (frame-shift mutagen), and UV light were used. Except for one experiment in which ethyl methanesulfonate only gave a marginal response, the mutagens consistently increased the frequency of BPr clones in a dose-dependent manner. A positive correlation was observed between the frequencies of thioguanine-resistant and BPr clones produced. Many BPr clones possessed considerably reduced, or undetectable AHH activities. Even in those variants that retained considerable AHH activity, heterogeneity in AHH activity among cells of the variants was relatively slight. The sensitivity of BPr variants to the mutagen used for their isolation is described. The in vitro temperature lability of AHH activity in certain BPr variants is discussed. (8 Refs)

31. CO-MUTAGENIC EFFECTS OF 2-AMINOANTHRACENE AND CIGARETTE SMOKE CONDENSATE ON SMOKER'S URINE IN THE AMES SALMONELLA ASSAY SYSTEM.

Hannan MA, Recio L, Deluca PP, Enoch H
McDowell Cancer Network, Univ. Kentucky, Lexington, KY, 40536
Cancer Lett; 13(3):203-212 1981

Cigarette smoke condensate (CSC), benzo[a]pyrene, and aromatic amine 2-aminoanthracene (2-AA) were shown to be indirect mutagens in the TA98 strain of Salmonella typhimurium. The combination of CSC and 2-AA had a synergistic effect on histidine reversion. The enhancement of the mutagenic activity of 2-AA by CSC in TA98 salmonella was dose-dependent. The co-mutagenic effect of SCS was shown to be specific. No co-mutagenic effect was exhibited when CSC was in combination with either ethylmethane sulfonate, methylmethane sulfonate, or 9,10-dimethyl-1,2-benzanthracene. In order to investigate the factor(s) in CSC that are responsible for the co-mutagenic activity in combination with 2-AA in a human body fluid, urine samples of cigarette smokers (2 packs/day) were tested in the Ames assay. Only the mutagenicity of 2-AA was enhanced by smoker's urine extract. Since the brand of cigarettes from which CSC was obtained was different from those smoked by the individuals who provided the urine samples, the results indicated that there is a co-mutagenic factor present in cigarette smoke. (20 Refs)

32. AN E COLI MICROSUSPENSION ASSAY FOR THE DETECTION OF DNA DAMAGE INDUCED BY DIRECT-ACTING AGENTS AND PROMUTAGENS.

McCarroll NE, Piper CE, Keech BH
Mutagenicity Section, Dept. Toxicology, Hazleton Lab. America, Inc., 9200 Leesburg Turnpike, Vienna, VA, 22180
Environ Mutagen; 3(4):429-444 1981

Seventy-seven compounds were examined for DNA-damaging activity in the Escherichia coli microsuspension assay (MSA). E coli strains WP2, WP2uvrA, CM611, WP67, WP100, W3110polA+, and p3478pola- were used. The noncarcinogen, 1-naphthylamine, which is weakly mutagenic in the Ames test and weakly genotoxic in the modified polA suspension assay, was negative in the MSA. No genotoxic activity was observed with 1-anthramine. It was suggested that the inactivity of the mutagenic carcinogens benzo(a)pyrene, 3-aminopyrene, and 4-nitrobiphenyl is related to the cell wall properties of E coli. Eight chemicals (mitomycin C, natulan, 5-bromo-2'-deoxyuridine, 5-fluoro-2'-deoxyuridine, thiacetarsamide, sodium arsenate, sodium arsenite, and sodium phenobarbital) which are not mutagenic in Salmonella were detected as DNA-modifying agents in the MSA. Six compounds (N-2-fluorenyl-acetamide, N-acetoxy-N-2-fluorenylacetamide, N-hydroxy-N-2-fluorenylacetamide, 2-nitrofluorene, 4-nitrobiphenyl, and benzo(a)pyrene) reported to be genetically active towards P3478 in a modified liquid suspension assay were negative in the MSA test with the DNA polymerase deficient strain. In this MSA, 77% of the 51 known or suspected carcinogens induced genetic damage in E coli and thus compared favorably with compilation appraisals of Salmonella assays. (35 Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

33. CHROMATOGRAPHIC-SPECTROMETRIC IDENTIFICATION OF AIRBORNE POLYNUCLEAR AROMATIC HYDROCARBONS.

Choudhury DR, Bush B
Div. Res. and Development, Richardson Vicks Inc., 1 Bradford Road, Mount Vernon, NY, 10553
Anal Chem; 53(9):1351-1356 1981

An integrated approach comprising a combination of glass capillary gas chromatography (GC), mass spectrometry (MS), liquid chromatography (LC), and UV spectrometry has been used for unambiguous identification of polynuclear aromatic hydrocarbons (PAH) in airborne particulates. Liquid chromatography with on-line UV spectral scanning was particularly valuable for differentiation and positive identification of isometric and coeluting PAHs. The advantages of this approach over GC/MS alone are illustrated. Parent PAHs containing three to seven rings were found in most samples examined, some alkly- and alkoxy-PAHs were also detected. A simple, one-step procedure for isolation of PAHs by preparative thin-layer chromatography is also reported. (Author abstract) (26 Refs)

REVIEWS AND OTHER POLYCYCLIC AROMATIC HYDROCARBON STUDIES

34. ENDOGENOUS CARCINOGENS.

Hill MJ
Bacterial Metabolism Res. Lab., Central Public Health Lab., London, England
Practitioner; 225(1356):803-804,807-809 1981

Estradiol is a potential endogenous carcinogen. Consuming a high fat/high energy diet, by increasing circulating estrogen levels and estrogen receptor activity, may increase the risk of carcinogenesis in estrogen-dependent tissues (breast, endometrium, possibly ovary). The role of cholesterol in carcinogenesis is not yet clear. The author's studies showed no relationship between fecal cholesterol levels and the risk of intestinal cancer in case-control studies. Some of the numerous urinary metabolites of tryptophan seem to be related to non-industrial bladder cancer. Intestinal bacteria can derive carcinogenic substances (ethionine, phenol, p-cresol, N-nitroso compounds, bile acid metabolites, etc) from dietary components and convert exogenous chemicals (eg, polycyclic aromatic hydrocarbons) to

proximate carcinogens. It is relatively easy to determine which carcinogens might be produced under ideal conditions, but there is limited information on which carcinogens are actually produced in vivo, and very little information regarding their importance. (27 Refs)

35. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).

De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981

The environmental, toxicological, and chemical aspects of PAHs are reviewed. Chrysene, 1,2-benzanthracene, 1,2-benzopyrene, 3,4-benzopyrene, o-phenylenepyrene, 3,4-benzofluoranthene, 10,11-benzofluoranthene, 1,2,3,4-dibenzopyrene, 3,4,8,9-dibenzopyrene, 3,4,9,10-dibenzopyrene, 1,2,5,6-dibenzacridine, and 1,2,7,8-dibenzacridine have been identified as carcinogenic PAH occurring in urban air. Benzo(a)pyrene, present in cigarette smoke, causes cancer in mammals after undergoing biotransformation to 7,8-diol-9,10-epoxide by microsomal enzymes. The latter substance was found to cause mutations in Chinese hamster cell cultures. The considerable increase in lung cancer mortality during the past 3 decades can be explained only partially by cigarette smoking, because air pollution must be made partially responsible. An increase in the benzo(a)pyrene level in the air by 1 ug/1,000 cubic meter is assumed to account for a 5% increase in the lung cancer mortality. (14 Refs) (In POR)

36. PULMONARY CARCINOGENESIS: ARYL HYDROCARBON HYDROXYLASE.

McLemore TL, Martin RR
Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Treat Res; 1:1-34 1981

Pulmonary carcinogenesis is discussed in relation to biochemical pathways for the metabolism of polycyclic aromatic hydrocarbons (PAHs) by human tissues, the activation of cigarette smoke PAHs by the aryl hydrocarbon hydroxylase (AHH) enzyme system, and the relation between tissue AHH levels and lung cancer susceptibility. The structure, function, and genetic control of the AHH system are described; and studies of AHH activity in peripheral blood lymphocytes, lung tissues, and pulmonary alveolar macrophages (PAMs) are reviewed. The theory that high AHH levels are related to lung cancer risk is supported significant differences in lymphocyte and PAM AHH levels in lung cancer and noncancer patients. (193 Refs)

37. SMOKING AND LUNG CANCER--NOW.

Huhti E
Dept. Medicine, Univ. Central Hosp., SF-90220 Oulu, Finland
Eur J Respir Dis; 62(3):147-149 1981

The relationship between smoking and lung cancer is summarized in the light of recent knowledge and suggestions concerning cigarette 'tar'. The tar contains important carcinogens such as benzo(a)pyrene (BP) and its metabolites. BP reactions with human lymphocyte DNA are known, and the smoke-induced DNA damage appears to be correlated with the risk of lung cancer. The tar content of cigarettes sold in the developed countries has decreased since the 1950s, and the carcinogenicity of the tar has been reduced. This explains why male smokers who died in the 1950s had more histologic changes in the bronchial epithelium than those who died in the 1970s. Both low-tar and filter cigarettes may be associated with reduced lung cancer mortality. The least detrimental cigarettes should be those with a medium nicotine yield (1.0-1.2 mg) and a tar content less than 10 mg. (20 Refs)

38. POLYCYCLIC AROMATIC HYDROCARBON OXIDATION DURING PROSTAGLANDIN BIOSYNTHESIS.

Marnett LJ
Dept. Chemistry, Wayne State Univ., Detroit, MI, 48202
Life Sci; 29(6):531-546 1981

Polycyclic hydrocarbons and other xenobiotics are cooxygenated during the oxidative metabolism of polyunsaturated fatty acids. The products of polycyclic hydrocarbon cooxygenation depend upon the hydrocarbon but they appear to be formed by radical (or electron transfer) mechanisms. The cooxygenations are hydroperoxide-dependent oxidations catalyzed by peroxidases and may be triggered by enzymes which biosynthesize fatty acid hydroperoxides. Prostaglandin endoperoxide synthetase is the principal hydroperoxide-generating system which has been studied to date. The extent to which polyunsaturated fatty acid-dependent cooxygenation operates in vivo is uncertain but preliminary studies suggest it does occur. (Author abstract) (113 Refs)

39. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

Since the oral mucosa is more resistant to the actions of chemical carcinogens than skin, early attempts to produce experimental malignant oral tumors were largely unsuccessful. The induction of squamous cell carcinomas in the thin lining mucosa of the hamster cheek pouch is discussed in detail, including the standardization the model, metastases, solvents, electron microscopy, histochemi stry, cell kinetics, co-carcinogenesis, nutritional status, and hormones. Problems associated with this model of carcinogenesis include the debate about whether the tissue is truly intraoral, that the cheek pouch is a site of immunological privilege, and the tissue is technically difficult to handle. Models of intra-oral carcinogenesis in extra-pouch sites include those using hamsters, mice, rats, and primates. The resistance of the oral mucosa to chemical carcinogens is discussed. At this time, the most suitable models of oral carcinogenesis are the hamster cheek pouch and tongue models using 9,10-dimethyl-1,2-benzanthracene and the rat palate model using 4-nitroquinoline N-oxide. (136 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. THE GENETIC TOXICOLOGY OF ALDRIN AND DIELDRIN.
Ashwood-Smith MJ
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Mutat Res; 86(2):233-242 1981

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Polycyclic Aromatic Hydrocarbons and Related Compounds

SERIES CK07 No. 82/02

FEBRUARY, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HUMAN EXPOSURE, DISTRIBUTION AND EPIDEMIOLOGY STUDIES

1. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981

The epidemiology of esophageal cancer (EC) is reviewed and epidemiological data are presented for a series of patients subjected to surgery for EC at a clinic during the period 1971-1980. The factors probably favorable for the development of EC are ethyl alcohol, tobacco, polycyclic aromatic hydrocarbons (benzopyrene, dibenzanthracene, and 3-methylcholanthrene) present in smoked foods, nitrosamines, molybdenum, tannin, hot food, diet deficient especially in thiamine, riboflavine, and vitamin C, esophageal stenosis, peptic reflux esophagitis, brachyesophagus, achalasia of the cardia, gastric resection, and Plummer-Vinson syndrome. The epidemiological analysis of the patients treated during the 1971-1980 period showed that all patients were in the age bracket 42-75 with a mean of 59.3 yr, and that women accounted for 5.2% of the patients only. Alcohol consumption (1 liter/day) was established in 18.5% of the patients, alcohol consumption and smoking (10 or more cigarettes/day) in 52.5%, smoking only in 18.5%, and neither smoking nor alcohol consumption in 10.5%. The cervical third of the esophagus was affected in 10.5% of all cases, the thoracic third in 34%, and the abdominal third in 55.5%. (28 Refs) (In ITA)

2. THE CHEMICAL AND BIOCHEMICAL CHARACTERIZATION OF PARTICULATE MATTER AS PART OF AN EPIDEMIOLOGICAL CANCER STUDY.

Wesolowski JJ, Flessel CP, Twiss S, Cheng J, Chan R, Garcia L, Ondo J, Fong A, Lum S
Air and Industrial Hygiene Lab., California Dept. Health Services, Berkeley, CA, 94704
J Aerosol Sci; 12(3):208-212 1981

During the winter season (November-February) 6-day high-vol glass filters were composited from each of 15 stations in Contra Costa County, California. Particulate matter was analyzed for total suspended particulate, benzene soluble organics (BSO), SO4, NO3, Pb, selected polycyclic aromatic hydrocarbons (PAH), and mutagenic activity. The five PAH, benzo(a)pyrene, benzo(ghi)perylene, benz(a)anthracene, chrysene, and coronene [a possible tracer for vehicle emissions], were quantitated by UV absorption an fluorescence. Mutagenicity was determined using the Ames test, with and without rat liver fraction S9. Since the correlation coefficients (Spearman) between mutagenicity (+S9) values and concentrations of the various PAH were only 0.33, 0.41, 0.36, 0.31 and 0.51, respectively, it is concluded that quantitation of the five PAH is not a good measure of air mutagenicity, which is consistent with the fact that these PAH constitute only about 2% of total air mutagenicity. Contour maps showing variations in air pollution will be useful for comparison of cancer incidence. The monitoring stations do provide some data on sources of pollution. High correlations between Pb, BSO and the five PAH implicate vehicles as a source. However, low correlations between mutagenicity (with or without S9) and these factors indicate mutagenicity may also derive from other sources. (12 Refs)

3. REASSESSMENT OF THE RELATIONSHIP BETWEEN ARYL HYDROCARBON HYDROXYLASE AND LUNG CANCER.

McLemore TL, Martin RR, Wray NP, Cantrell ET, Busbee DL
(c/o Busbee) Dept. Biology, Genetics Center, North Texas State Univ., Denton, TX, 76203
Cancer; 48(6):1438-1443 1981

Aryl hydrocarbon hydroxylase was measured in cultured human WBC induced with benzathracene and in pulmonary alveolar macrophages induced in situ in cigarette smokers. Considered separately, neither WBC AHH nor macrophage AHH levels were distinctly different in either noncancer or lung cancer patients. Considered simultaneously, WBC and macrophage AHH levels are quite different in noncancer and lung cancer patients. The lung cancer patient group was seen to contain a significantly higher percentage of persons with high levels of AHH than did an age-matched group of noncancer patients, (p less than 0.001), when more than one tissue was assayed to determine the individual's enzyme levels. (Author abstract) (42 Refs)

UPTAKE AND METABOLISM

4. BILIARY EXCRETION, SYSTEMIC AVAILABILITY AND REACTIVITY OF METABOLITES FOLLOWING INTRAPORTAL INFUSION OF [3H]BENZO[A]PYRENE IN THE RAT.

Chipman JK, Frost GS, Hirom PC, Millburn P
Dept. Biochemistry, St. Mary's Hosp. Medical Sch., Norfolk Place, London W2, England
Carcinogenesis; 2(8):741-745 1981

[3H]Benzo-a-pyrene (BP) was introduced by intraportal infusion into male Wistar rats. Doses were either 5 or 0.125 umole/kg body wt over a period of 3 min. BP metabolites in the blood, bile, and liver were analyzed. For both dose levels the amount of [3H] directly extractable from bile with ethyl acetate was 14.9-18.2% of the [3H] present. After treatment with beta-glucuronidase 24-30% was extractable from the bile. The amount of [3H] extractable from the blood with ethyl acetate was 64.5% with a BP dose of 0.125 umole/kg and 79.6% with a dose of 5.0 umole/kg. The corresponding amounts from the liver were 69.7% and 82.0%, respectively. At higher doses the proportion of the dose remaining in the liver was lower than at lower doses. [3H] extracted from the liver represented mainly unchanged BP, while that extracted from the bile represented mainly metabolites. A high pressure liquid chromatography profile showed the occurrence of relatively more BP 1,6-quinone and BP 6,12-quinone at the lower dose and more 4,5-dihydrodihydroxy benzo[a]pyrene at the higher dose. Measurement of covalent binding of [3H]BP-derived radioactivity to hepatic protein and DNA showed the binding to be 5-20-fold greater in protein than in DNA. The results indicated no saturation of the detoxification mechanisms in the rat. The escape of BP and its metabolites into the systemic blood was indicated, suggesting that potentially reactive metabolites may reach extrahepatic sites. (24 Refs)

5. METABOLISM OF CHEMICAL CARCINOGENS BY CULTURED HUMAN AND RAT BLADDER EPITHELIAL CELLS.

Autrup H, Grafstrom RC, Christensen B, Kieler J
Lab. Environmental Carcinogenesis, Copenhagen, Denmark
Carcinogenesis; 2(8):763-768 1981

Cells from human bladder epithelium cell lines HU1689, HU1752, and HU1765 and primary bladder epithelial cells from Wistar rats were exposed in vitro for 24 hr to radioactively-labeled carcinogens dissolved in the medium: [1,3,6-3H]benzo[a]pyrene (BP) 1.5 uM; [G3H]aflatoxin B1 (AFB) 1.5 uM; [14C]N-nitrosodimethylamine (DMNA) 100 uM; [ethyl-1-14C]N-nitrosoethylmethylamine (EMNA) 100 uM; and [2,5-14C]N-nitrosopyrrolidine (NPy) 100 uM. The metabolism of the carcinogens was assayed by the release of metabolites into the culture medium and the binding of radioactive metabolites to DNA. The human bladder cells retained 2 the capacity to metabolize chemical carcinogens. Binding of DNA occurred to a similar extent in all three cell lines. More BP was bound to DNA in human bladder cells than in rat bladder cells. More than 90% of the metabolites of BP in human cells consisted of organo-soluble products, primarily the 9,10-and 7,8-BP diols. N-nitrosamine metabolism produced CO2. NPy was oxidized in both the alpha and beta positions, predominantly alpha in human cells. EMNA was apparently metabolized, but did not bind to DNA. The results suggest that the human bladder may be able to activate carcinogens that come into direct contact with the epithelium, and that it utilizes pathways that are different from those found in other tissues and cells. (38 Refs)

BINDING TO CELLULAR MACROMOLECULES

6. UPTAKE OF LIPOPHILIC CARCINOGENS BY PLASMA LIPOPROTEINS. STRUCTURE-ACTIVITY STUDIES.

Shu HP, Nichols AV
Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720
Biochim Biophys Acta; 665(3):376-384 1981

This report describes the interaction between plasma lipoproteins and two hydroxylated metabolites of benzo[a]pyrene, 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-7,8-dihydrodiol, which differ significantly in lipophilicity. When incubated with plasma, the metabolites of benzo[a]pyrene exhibit a decreasing distribution into the ultracentrifugal lipoprotein fraction (d less than or equal to 1.20) and an increasing distribution into the albumin-rich fraction (d greater than 1.20) as the degree of hydroxylation of the metabolite increases. At saturation, uptake of benzo[a]pyrene by VLDL, LDL and HDL correlates with lipoprotein total-lipid vol. Uptake of hydroxylated derivatives per lipoprotein total-lipid vol, in general, decreases with increasing hydroxylation. Contrary to this trend, HDL uptake of 3-hydroxybenzo[a]pyrene at saturation is significantly higher than its uptake of benzo[a]pyrene. Uptake of benzo[a]pyrene-7,8-dihydrodiol per total-lipid vol by all of the lipoprotein classes at saturation is considerably lower than their uptake of 3-hydroxybenzo[a]pyrene. Factors in addi tion to lipid solubility substantially alter lipoprotein uptake of the metabolites. (Author abstract) (15 Refs)

7. THE FORMATION AND PERSISTENCE OF BENZO(A)PYRENE METABOLITE-DEOXYRIBONUCLEOSIDE ADDUCTS IN RAT SKIN IN VIVO.

Ashurst SW, Cohen GM
(c/o Cohen) Toxicology Unit, Sch. Pharmacy, Univ. London, 29/39 Brunswick Square, London, England
Int J Cancer; 28(3):387-392 1981

The extent of reaction of benzo(a)pyrene with DNA and the formation of benzo(a)pyrene-deoxyribonucleoside adducts in the skins of male Wistar rats were investigated. Following topical application of benzo(a)pyrene (200 nmoles), binding reached a max of 0.74 pmoles/mg DNA, 12 hr after treatment, and remained high up to 48 hr after treatment. Hydrolysis of the DNA and analysis of the deoxyribonucleoside adducts by HPLC revealed several products. The major adduct, C, (27-40% of the total adducts), co-chromatographed with deoxyribonucleoside adducts formed by reaction of (+-)7beta, 8alpha-dihydroxy-9alpha, 10alpha-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (anti BPDE) with DN*, whilst product B, (19-23% of the total adducts), also formed in significant amounts, co-chromatographed with a further metabolite of 9-hydroxybenzo(a)pyrene bound to an as yet undetermined base in the DNA. Smaller amounts of other deoxyribonucleoside adducts, D and I, were also observed and co-chromatographed with marker compounds derived from reaction of anti BPDE with deoxyadenosine and (+-)7beta, 8alpha-dihydroxy-9beta, 10beta-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (Syn BPDE) with DNA respectively. There was no evidence for preferential removal of any of the four adducts (B, C, D, and I) during the 48 hr after treatment with benzo(a)pyrene. The relative resistance of rat skin, compared with mouse skin, to benzo(a)pyrene-induced skin carcinogenesis may be due in part to a lower extent of binding of benzo(a)pyrene to DNA, and a smaller percentage of both methanol-soluble hydrocarbon-deoxyribonucleoside adducts and of adducts derived from the putative ultimate carcinogen, BPDE. (Author abstract) (36 Refs)

8. DIFFERENCES IN THE BINDING OF 3-METHYLCHOLANTHRENE AND PHENOBARBITAL TO RAT LIVER CYTOSOLIC AND NUCLEAR PROTEIN FRACTIONS.

Tierney B, Bresnick E
Dept. Biochemistry, Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Arch Biochem Biophys; 210(2):729-739 1981

In an effort to learn more about the induction of cytochromes P-450c and P-450b, two inducers of these cytochromes, 3-methylcholanthrene (3-MC) and phenobarbital (PB), respectively, were studied in their interactions with proteins from rat serum, rat liver cytosol, and rat liver nuclei. Using DNA-cellulose chromatography, it was demonstrated that 3-MC binds to both cytoplasmic and nuclear components (at approx 27 and 250-570 femtomole/mg of applied protein, respectively) and that PB does not bind to proteins from serum, cytosol, or nuclei that can bind to this chromatographic medium. No binding of PB to cytosolic proteins was demonstrated using DEAE A-50 Sephadex chromatography, charcoal dextran analysis, or sucrose density gradient centrifugation, but the binding of 3-MC to cytosolic proteins gave four peaks of radioactivity by the DEAE technique, two peaks by the sucrose gradient technique, and a specific binding of 0.13 picomole/mg protein by charcoal dextran analysis. One of the sucrose gradient peaks was labile in the presence of 0.3 M KCl, its disappearance

being accompanied by an increase in the amplitude of the other peak. Following incubation with whole nuclei, the uptake and intranuclear distribution of 3-MC and PB differed markedly: 64% of the available 3-MC radioactivity but only 3% of the available PB radioactivity became associated with nuclei; moreover, the highest specific activity of this radioactivity was found in different locations, ie, associated with the 2 M KCl-resistant nuclear pellet for 3-MC and with the nuclear fraction soluble in the absence of salt for PB. Nuclear proteins that can bind to both polycyclic hydrocarbons and to DNA have not previously been reported. (43 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS INDUCED BY POLYCYCLIC AROMATIC HYDROCARBONS

9. COMPARISONS OF THE EFFECTS OF CHEMICAL CARCINOGENS IN MIXED CULTURES OF RAT HEPATOCYTES AND HUMAN FIBROBLASTS.

Strom S, Kligerman AD, Michalopoulos G
Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
Carcinogenesis; 2(8):709-715 1981

Human male diploid fibroblasts (strain GM 3468) and parenchymal hepatocytes from male Sprague Dawley rats were treated separately and in mixed cell cultures with benzo[a]pyrene (BP), diethylnitrosamine (DEN), or 2-acetylaminofluorene (AAF). Fibroblast DNA was prelabeled with 5-bromo-2'-deoxyuridine. After exposure to the carcinogens, fibroblast and hepatocyte DNA was analyzed for unscheduled DNA synthesis (UDS). Fibroblast and hepatocyte DNA from mixed cultures was separated by isopycnic centrifugation in neutral cesium chloride. The hepatocarcinogens DEN and AAF produced increased UDS in hepatocytes, but not in fibroblasts, either separately or in mixed cultures. BP, a non-hepatocarcinogen, produced more UDS in in fibroblasts than in hepatocytes in mixed cultures. More BP was bound to fibroblast DNA than to hepatocyte DNA. BP bound to DNA from cultures of fibroblast alone was about 30% of that bound to fibroblast DNA from mixed cultures. BP produced no UDS in fibroblast in the absence of hepatocytes. Evidently the hepatocytes activated the UDS-promoting capacity of BP, which then was passed to the fibroblasts. The results obtained with BP, DEN, and AAF correspond to previous in vivo observations of the tissue-specific carcinogenicity of the three agents. The possibility that intercellular distribution may play a role in carcinogenic effects is indicated. (37 Refs)

10. CLASSIFICATION OF CHEMICAL AGENTS AS TO THEIR ABILITY TO INDUCE LONG- OR SHORT-PATCH DNA REPAIR IN HUMAN CELLS.

Francis AA, Snyder RD, Dunn WC, Regan JD
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 83(2):159-169 1981

The excision repair response of normal human fibroblasts (NHF) and of xeroderma pigmentosum (XP) cells to 33 chemicals was compared with that to UV irradiation (which is known to induce 'long-patch' repair of about 90 nucleotides) and to gamma irradiation (which is known to induce 'short-patch' repair of 3-4 nucleotides) by the 5-bromodeoxyuridine (BrdU) photolysis assay that quantitates unscheduled DNA synthesis. The following chemicals induced long-patch repair of 30-70 nucleotides in length and may be classified as UV-mimetic agents: N'-acetoxyacetylaminofluorene, ICR-170, 4-nitroquinoline-1-oxide, diarylcarbamate, 7-bromomethylbenzanthracene, dimethylbenzanthracene-5,6-epoxide, 7beta,8alpha-diol-9beta,10beta-epoxybenzo[a]pyrene, 7beta,8alpha-diol-9alpha,10alpha-epoxybenzo[a]pyrene, ethyl methanesulfonate, methyl methanesulfonate, and N-hydroxy-1-naphthylamine. The other chemicals elicited short-patch repair in NHF cells; the measurable DNA repair activity was at the limit of resolution of the sucrose density gradient technique employed to assay it. XP cells could not repair damage by these latter chemicals to the same extent that NHF cells could. It appears that, for the chemicals tested here, the ability of an agent to elicit a long-patch DNA repair response from NHF is a property of the most active direct-acting carcinogens. (23 Refs)

11. EFFECT OF BENZO(A)PYRENE AND ITS NONCARCINOGENIC ANALOG 1,2-BENZOPYRENE ON NA,K-ATPASE ACTIVITY OF HOMOGENATES OF VARIOUS MOUSE ORGANS AND OF MEMBRANE PREPARATION FROM RAT HEART.

Mustafin AM, Kim SCh
Kazakh Inst. Oncology and Radiology, Alma-Ata, USSR
Biull Eksp Biol Med; 91(7):76-77 1981

The effect of benzo(a)pyrene (BP) and its noncarcinogenic analog 1,2-benzopyrene (1,2-BP) on Na, K-ATPase activity was studied in homogenates of albino mice lungs, stomach, and liver. BP caused significant inhibition of enzyme activity in the lungs and in the stomach; the inhibitory effect of 1,2-BP was less pronounced. Both BP and 1,2-BP did not inhibit the enzyme activity of liver homogenate and activity of Na ,K-ATPase from the membranes of rat heart. (5 Refs) (In RUS)

FACTORS MODIFYING THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

12. MOUSE SKIN CELLS RESISTANT TO TERMINAL DIFFERENTIATION ASSOCIATED WITH INITIATION OF CARCINOGENESIS.

Yuspa SH, Morgan DI
Lab. Experimental Pathology, NCI, Bethesda, MD, 20205
Nature; 293(5827):72-74 1981

The dorsal epidermis of 7-8-wk-old BALB/c and SENCAR mice in the resting phase of the hair cycle was painted once with a tumor-initiating dose of 7,12-dimethylbenz[a]anthracene (DMBA; 25 ug/200 ul acetone) followed by 5 ug of the promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA) in 200 ul acetone, 2 x/wk for 4 wk beginning 7 days after DMBA application. Controls received acetone only. Either 3 days or 1 wk after the last application of TPA or acetone, the mice were sacrificed and their dorsal skin cultured under conditions that permit selection of differentiation-resistant foci. Only 2/99 dishes derived from epidermis of noninitiated BALB/c mice with or without TPA contained foci resistant to Ca++-induced terminal differentiation, and the colonies were very small and relatively pale, whereas 50-60% of the dishes derived from initiated BALB/c mice contained differentiation-resistant colonies that were mostly either confluent or dark red, and large. The SENCAR line, bred for sensitivity to skin carcinogenesis, behaved differently: dishes derived from epidermis of

noninitiated mice with and without TPA and dishes derived from epidermis of initiated and promoted mice showed equal numbers of positive results (7/29 plates), while dishes from initiated, unpromoted mice yielded approx 60% (18/30) positive plates. Thus, SENCAR epidermis appears to contain preexisting initiated cells; the reduction of positive plates in the initiated and promoted group may have been due to cytotoxicity associated with TPA application in this mouse strain. The differentiation-resistant assay reported here appears to be of use in recognizing and quantitating the alteration in regulation of normal differentiation that is postulated to be an early event in chemical carcinogenesis. (17 Refs)

13. INHIBITION OF DMBA CARCINOGENESIS OF HAMSTER BUCCAL POUCH BY PHENANTHRENE AND DIMETHYLNAPHTHALENE.

Malament DS, Shklar G

Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, Boston, MA, 02115

Carcinogenesis; 2(8):723-729 1981

Eighty male and female young adult golden Syrian hamsters were divided into four groups. Group A was the control group. Groups B, C, and D were treated by painting of the left buccal pouch three times per wk. Group B was painted with a 0.5% soln of 7,12-dimethylbenz[a]anthracene (DMBA) in heavy mineral oil. Group C was painted with mineral oil containing 0.3% 1,4-dimethylnaphthalene (DMN) and 0.5% DMBA. Group D was painted with mineral oil containing 0.3% phenanthrene (Phe) and 0.5% DMBA. Rats from each group were sacrificed at 8, 10, 12, 14, and 16 wk. The buccal pouches, heart, lungs, liver, spleen, kidneys, and adrenals were studied. Group A showed no tumors. Group B showed early invasive carcinoma of the buccal pouch with ulcerations. Group D showed significant reduction in the number of tumors and in tumor size over gr oup B, without ulceration. Group C showed intermediate tumor numbers and sizes. Apparently Phe, and to a lesser extent DMN, retard the development of epidermoid carcinomas in hamster buccal pouches induced by DMBA. (35 Refs)

14. GLUCOCORTICOIDS AND BENZO(A)PYRENE HAVE OPPOSING EFFECTS ON EGF RECEPTOR BINDING.

Ivanovic V, Weinstein IB

Div. Environmental Sciences and Cancer Center/Inst., Cancer Res. Columbia Univ., Coll. Physicians and Surgeons, 701 West 168th St., New York, NY, 10032

Nature; 293(5831):404-406 1981

Epidermal growth factor (EGF)-receptor binding was used as a marker for membrane effects in C3H10T1/2 mouse embryo fibroblasts exposed to the potent glucocorticoid fluocinolone acetonide (FA), and to the carcinogens benzo(a)pyrene (BP), and 12-O-tetradecanoyl-phorbol-13-acetate (TPA). FA alone produced a 1.9x stimulation of EGF-receptor binding over that observed in control cultures. The stimulation was apparent within 1 hr and reached a max by 24 hr. FA pretreatment (2 x 10(-7) M) protected the cells from the approx 50% inhibition of EGF-binding induced by BP (2 x 10(-6) M) or TPA (10(-9) M). Results suggested that glucocorticoids inhibit carcinogenesis by inducing cell membrane changes that are reciprocal to those induced by carcinogens and tumor promotors. (22 Refs)

15. PROPHYLAXIS OF 3-METHYLCHOLANTHRENE-INDUCED TUMORIGENESIS IN MICE WITH THE YEAST POLYSACCHARIDE PREPARATION.

Kumano N, Kikumoto T, Koinumaru S, Nakai Y, Ishikawa T, Suzuki S, Konno K

Dept. Internal Medicine, Res. Inst. for Tuberculosis and Cancer, Tohoku Univ., Sendai 980, Japan

Tohoku J Exp Med; 134(4):401-409 1981

The protective effect of a Candida utilis glucomannan preparation (YPS) on 3-methylcholanthrene-induced sarcoma formation was studied in male ddI and C3H/He mice. ddI mice received 10 or 30 doses of YSP (100 mg/kg/day, ip) according to a schedule that was either completed or initiated from 1 or 14 days before or after MCA (0.5 mg, sc) administration. CeH/He mice received YPS (10 or 100 mg/kg, ip) beginning the day after MCA treatment. YPS had no effect on the cumulative tumor incidence in ddI mice, but it significantly prolonged the latent period before tumor appearance. This protection was achieved with all pre- and posttreatment schedules, although the one delayed for 2 wk after MCA was only marginally effective. Tumor incidence in the treated groups was less than 50% on day 100, but it reached 100% on day 150. The longer latency due to YPS treatment was associated with faster tumor growth and a short life span than found in untreated controls. C3H/He mice did not respond to YPS treatment; in both treated animals and controls, tumor incidence reached 100% by 120 days after MCA administration. (19 Refs)

16. EFFECT OF NOCARDIA RUBRA CELL-WALL SKELETON TREATMENT ON TUMOR FORMATION IN TWO- STAGE CHEMICAL CARCINOGENESIS OF MOUSI SKIN.

Inoue T, Yoshimoto T, Ogura T, Hirao F, Azuma I, Yamamura Y

The Third Dept. Internal Medicine, Osaka Univ. Medical Sch., Fukushima 1-1-50, Fukushima-ku, Osaka 553, Japan

Cancer Immunol Immunother; 11(3):207-210 1981

Male C57BL/6 mice were painted at age 11 wk on the dorsal skin with 20 ug 7,12-dimethylbenz[a]anthracene (DMBA). Beginning 7 wk later they were painted with 2.5 ug 12-O-tetradecanoyl-phorbol-13-acetate (TPA) 2x/wk for 30 wk. Three groups of mice were treated with sc injections of 100 ug Nocardia rubra cell-wall skeleton (N-CWS) 1x/wk for 7 wk. Group 1 received the N-CWS before initiation with DMBA. Group 2 received N-CWS between initiation and promotion with TPA. Group 3 received N-CWS beginning at the start of promotion. A fourth group recieved no N-CWS treatment. All N-CWS-treated groups showed prolongation of the latent period before appearance of the first tumor. Group 1 exhibited the most significant reduction in incidence of skin tumor (5/17 30 wk from the beginning of promotion vs 13/19 in Group 4) and number of tumors/survivor (0.35 at 30 wk vs 1.74 in Group 4). N-CWS was effective in group 3 until 20 wk after the beginning of promotion. It was also effective in group 2 at 15 wk after the beginning of promotion, but overall tumor yield was the same in groups 2 and 4. N-CWS may inhibit carcinogenesis by enhancing immunological surveillance at the promotion stage or by activating macrophages which sequester DMBA. (24 Refs)

17. TUMOR PROMOTION BY FOREIGN BODIES (IUD).

Ryan WL, Stenback F, Curtis GL
Dept. Biochemistry, Univ. Nebraska Medical Center, South Lab., Room 3018, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Lett; 13(4):299-302 1981

The effect of implanted commercial intrauterine device (IUD) fragments on production of tumors initiated with 7,12-dimethylbenzanthracene (DMBA) was studied in strain A female mice. Two wk after sc or ip insertion of 4-7 mm Lippes Loop or Cu-7 IUD fragments, topical DMBA application (25 ug qod) in the shaved interscapular area was begun, for a total of 200 ug DMBA/mouse. Treatment groups received (1) DMBA only, (2) DMBA + Lippes Loop sc, (3) DMBA + Lippes Loop ip, or (4) DMBA + Cu-7 ip. Respective rates of mice having tumors were 20% (2 papillomas, 2 keratoacanthomas, mean size 19 square mm (mm2)), 33% (4 papillomas, 1 squamous cell carcinoma, 1 gross identification only, size 20 mm2), 60% (9 papillomas, 1 keratoacanthoma, 3 squamous cell carcinomas, 4 gross identification, size 38 mm2), and 66% (19 papillomas, 5 squamous cell carcinomas, 1 gross identification, size 40 mm2). Tumor development in groups 3 and 4 was significantly different from that in group 1; tumor appearance was faster (8 and 10 wk, respectively, vs 16 wk) and tumor size was twice as large. IUDs employed as foreign bodies apparently promote skin carcinogenesis by the ca rcinogen DMBA. The result is particularly striking when the IUD is implanted ip; evidently, promotion and initiation need not occur in the same place. Autoantibodies may be one of the means of tumor promotion. (9 Refs)

TUMORIGENICITY, MUTAGENICITY AND IN VITRO TRANSFORMATION STUDIES

18. CARCINOGEN-DNA ADDUCTS IN MUTAGENESIS ASSAYS.

Bigger CA, Dipple A, Tomaszewski JE, Lake RS
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Science; 213(4514):1411-1412 1981

Comparative studies of carcinogen metabolism in different systems to examine the assumption that the subcellular Aroclor-induced rat liver metabolizing system, recommended for general mutagenesis screening, effectively duplicated the activation of carcinogens in target tissue in vivo are described. In a series of studies, it was demonstrated that DNA-reactive metabolites of 7,12-dimethylbenz(a)anthracene generated by Aroclor-induced rat liver microsomes or S9 fraction differ substantially from those generated in intact cellular systems in vitro and a target tissue, mouse skin, in vivo. Studies with aflatoxin B1 and benzo(a)pyrene show no DNA adduct data for the Arochlor-induced rat liver system. It was suggested that the specific DNA adducts responsible for carcinogenesis are not known with certainty for any carcinogen, but that there is evidence to show that specific DNA reactive metabolites play a central role in carcinogenesis. Because of the wide application of these liver homogenates as models of in vivo activation in in vitro systems for the detection of potential carcinogens whose structure, pathways of metabolism, and mechanism of action are unknown, it was suggested that the accurate reproduction of in vivo activation cannot be assumed. (9 Refs)

19. RAT HEPATOCYTE-MEDIATED MUTAGENESIS OF HUMAN CELLS BY CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS BUT NOT ORGANOCHLORINE PESTICIDES.

Tong C, Fazio M, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Proc Soc Exp Biol Med; 167(4):572-575 1981

The establishment of a hepatocyte primary culture-mediated human cell hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutagenesis assay is reported. In the rat hepatocyte primary cultures (HPC)-mediated Detroit 550 (D-550) HGPRT mutation assay, 1 x 10(6) D-550 were generally coplated with 20 x 10(6) freshly prepared HPC. The cocultures were allowed to attech for 2 hr, were washed, and fresh media containing the carcinogens or appropriate controls were added for 24 hr exposure. The cultures were washed then allowed to grow for 10 days to allow mutant expression. In general, by day 4, no viable HPC were observed. HGPRT mutants were selected in the human foreskin cell line D-550 by 6-thioguanine (TG). Exposure of D-550 alone to benzo(a)pyrene or 7,12-dimethylbenz(a)anthracene did not result in any increase in TG-resistant (TGr) mutant incidence over the parallel-run control. However, a significant increase in the TGr mutant incidence over that in control cultures occurred in D-550 when the carcinogen exposure was in the presence of HPC. With dichlorodiphenyltrichloroethane, chlordane, and mirex, no significant increase in TGr mutant incidence was observed in the exposed human cells either in the presence or absence of HPC. An epigenetic mechanism for the carcinogenicity of these organochlorine pesticides is suggested. (34 Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

20. RECOVERY AND FLUOROMETRIC MEASUREMENT OF A POLYNUCLEAR AROMATIC HYDROCARBON FROM SMOKED CIGARETTES.

Attiyat AS, Christian GD, Callis JB
Dept. Chemistry, Yarmouk Univ., Irbid, Jordan
Microchem J; 26(3):344-353 1981

The recovery of the polynuclear aromatic hydrocarbon (PAH) perlene from cigarette smoke condensate (CSC) and cigarette filters was studied by fluorescence spectroscopy. Six commercial filter cigarettes that had been spiked with 2, 4, 6, 8, 10, and 20 ug of perlene, respectively, were smoked on a smoking machine. The fluorescence spectra and the Shpol'skii spectra of the spiked samples showed large peaks characteristic of perlene, which were essentially absent from the solvent and the control. The analytical recovery of perlene from CSC and filters was shown to be 68.4% and 81.4% of the added amount, respectively. The actual recovery of perlene from CSC and filters combined (corrected for the analytical recovery) ranged between 34 and 72%, that in CSC was between 3 and 24% and that in filters between 17 and 69%; the percentage recovered from CSC increased with the amount added up to about 10 ug and then became constant. The analytical precision was excellent; the coefficient of variation was 6% (n = 4) in the filters and 36% (n = 3) in the CSC. These results demonstrate that this technique can be used to follow that fate of PAH in biological systems. (23 Refs)

21. APPLICATION OF A GEOMETRIC PARAMETER DEFINING MOLECULAR SHAPE, FOR THE QUANTITATION OF INTERACTION OF POLYCYCLIC AROMATIC HYDROCARBONS WITH ENZYME SYSTEMS.

Lamparczyk H, Radecki A, Kaliszan R
Faculty Pharmacy, Medical Academy, K. Marksa 107, 80-416 Gdansk, Poland
Biochem Pharmacol; 30(16):2337-2341 1981

Quantitative relationships between the ability of polycyclic aromatic hydrocarbons to induce and repress various enzyme systems and a geometric parameter expressing their molecular shape have been described. In contrast, no statistically significant relationship was found when quantum-chemical parameters characterizing the reactivity and donor-acceptor properties of these compounds were correlated with their biological activity. (Author abstract) (17 Refs)

22. OPTICALLY DETECTED MAGNETIC RESONANCE EVIDENCE FOR CARCINOGEN-NUCLEIC ACID INTERACTION IN THE TETRAHYDRO-9,10-EPOXYBENZO[E]PYRENE-DNA ADDUCT.

Lefkowitz SM, Brenner HC
(c/o Brenner) Dept. Chemistry, New York Univ., New York, NY, 10003
J Am Chem Soc; 103(17):5257-5259 1981

The carcinogenic action of polycyclic aromatic hydrocarbons evidently is mediated by metabolically-activated intermediates which bind covalently to DNA. The optically-detected magnetic resonance technique was used to study the structure of the adduct of tetrahydro-9,10-epoxybenzo[e]pyrene (BePE) with DNA. The pyrene triplet chromophore in the BePE-DNA adduct appears to exist in an environment intermediate between complete intercalation and complete solvent exposure. (21 Refs)

REVIEWS AND OTHER POLYCYCLIC AROMATIC HYDROCARBON STUDIES

23. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.

Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

Elucidation of the structures of active polycyclic aromatic hydrocarbon metabolites and of the pathways leading to their formation are reviewed with respect to implications for the mechanism of cancer induction. Major topics discussed include metabolism, K-region arene oxides, diol epoxide metabolites of other polyarenes, diol epoxide-nucleic acid interaction, and theories of carcinogenesis. Although much is now known in the areas of metabolic activation and tumor initiation, unanswered questions remain concerning the relation of DNA alkylation and tumor induction, regioselectivity of alkylation, fidelity of transcription, and nucleic acid repair and errors during repair. (123 Refs)

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CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).
De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.
Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?
Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.
Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.
Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
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7. RADIOACTIVITY IN DRINKING WATER.
Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.
Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

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IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
In ITA

10. PANCREATIC CANCER.
Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.
Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.
Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
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13. INDUSTRIAL CARCINOGENESIS.
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Zh Eksp Klin Med; 21(3):287-292 1981
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16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.
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Institutul de igiena si sanatate publica, Iasi, Romania
Igiena; 30(1):1-9 1981
In RUM

17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.
Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.
Lasbes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

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Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

20. PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND. (ONCOLOGY OVERVIEW)
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Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.
Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.
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Res. Lab. Experimental Immunobiology, Moscow, USSR
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23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.
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24. BURKITT'S LYMPHOMA.
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25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.
Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

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26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.
Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

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Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.
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Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.
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Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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CHEMICAL CARCINOGENESIS

Polycyclic Aromatic Hydrocarbons and Related Compounds

SERIES CK07 No. 82/03 MARCH, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. ENVIRONMENTAL POLLUTION WITH CARCINOGENIC HYDROCARBONS DURING AIRPLANE FUEL COMBUSTION.

Smirnov GA, Khesina Alla, Khorvat A, Kertes M
All-Union Cancer Res. Inst., Moscow, USSR
Gig Sanit; (8):78 1981

To determine the potential sources of environmental pollution with carcinogenic hydrocarbons, benzo(a)pyrene (BP) level was studied in the area of airplane take-off strip. Increased BP level was recorded both in the soil and in the air. (3 Refs) (In RUS)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

2. DIFFERENTIAL EFFECT OF SEVERAL INDUCERS ON HEPATIC AND MAMMARY BENZO(A)PYRENE METABOLISM IN RAT AND HAMSTER.

Gingell R, Weber A, Ilacqua V, Van de Walle C, Hertzog P
Shell Development Co., Westhollow Res. Center, P. O. Box 822, Houston, TX, 77001
Drug Chem Toxicol; 4(2):101-112 1981

The ability of female Sprague Dawley rat and Syrian golden hamster mammary microsomes, as compared with the liver, to metabolize benzo(a)pyrene (BP) was examined in an attempt to understand the different susceptibilities of these species to polynuclear hydrocarbon-induced mammary tumorigenesis. The effect of pretreatment with several known mixed function oxidase inducers on these activities was studied in both species. Control hamster hepatic benzo(a)pyrene-hydroxylase (BPH) activity was considerably greater than that of the rat. Aroclor was the only inducer to significantly increase hamster hepatic BPH activity, and this by only two-fold. 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene had no effect on hamster liver BPH activity while beta-naphthoflavone (BNF) slightly inhibited this activity. All compounds examined were potent inducers of hepatic BPH and cytochrome P450 in the rat. Control hamster mammary microsomal BPH activity was much lower than the hepatic level, but was four-fold greater than the corresponding level for the rat. All the pretreatments caused similar increases in mammary activity in both species, BNF being the most effective. The ability of control hamster hepatic microsomes to metabolize BP was considerably greater than for the rat. The results indicated that rat and hamster mammary gland microsomes, as well as those of liver, are capable of metabolizing BP. All the pretreatments investigated induced mammary activity in both species, but the rat activity was more inducible than that of the hamster. It was therefore suggested that metabolic activation of carcinogenic polycyclic hydrocarbons can occur in the mammary gland itself. (16 Refs)

3. ENZYMATIC METHYLATION OF MICROSOMAL METABOLITES OF BENZO(A)PYRENE.

Lombardi PE, Mayhew JW, Goldin BR, Gregory ME, Lynch MA, Sullivan CE, Gorbach SL
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Cancer Res; 41(11,part1):4415-4419 1981

These studies suggest that the microsomal metabolism of benzo(a)pyrene (BP) produces metabolites which can be methylated by the catechol-o-methyltransferase (COMT)/S-adenosylmethionine (SAM) enzyme/donor combination. Induced microsomes converted 12 to 15% of substrate BP to polar products. Approx 0.06% of substrate BP was recovered as COMT/SAM-reactive substances. In tests for specificity, COMT/SAM was found to react with catechols, but not with dihydrodiols, quinones, a phenol, an epoxide, or 1,4-hydroquinone. Organic extracts of COMT/[14C]SAM incubations with BP were fractionated by high-performance liquid chromatography. The appearance of radiolabeled chromatographic bands required the presence of substrate BP, microsomes, and COMT/[14C]SAM. When the Ames mutagenesis assay was supplemented with COMT/SAM, a 36% reduction was observed in the number of revertant colonies induced by the microsomal oxidation of BP. In contrast, the mutagenic properties of 2-aminofluorene were not affected by COMT/SAM. These observations indicate that COMT/SAM does not generally inhibit mixed-function oxidase activity but rather reacts with substances which are activated by ring oxygenations. (Author abstract) (33 Refs)

4. METABOLISM OF BENZO[A]PYRENE IN RAT PROSTATE GLANDS FOLLOWING 2,3,7,8-TETRACHORODIBENZO-P-DIOXIN EXPOSURE.

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Lab. Reproductive and Developmental Toxicology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Carcinogenesis; 2(9):823-831 1981

Benzo(a)pyrene (BP) metabolism was studied in the prostate glands of adult Sprague-Dawley rats treated with the potent monooxygenase inducer 2,3,7,8-tetrachorodibenzo-p-dioxin (TCDD: 2.5, 5, or 10 ug/kg, po). TCDD not only caused selective induction of prostatic aryl hydrocarbon hydroxylase (AHH) and cytochrome P-446, but also resulted in a significant increase in organic-soluble BP metabolites over aqueous conjugated metabolites. High-pressure liquid chromatography analysis showed that formation rates of phenols, quinones, and dihydrodiols in TCDD-induced prostate glands were, respectively, 290, 192, and 38 times higher than in noninduced glands. The rate of 7,8-diol formation was 1.5 times that of 4,5-diol and 3 times that of 9,10 diol. TCDD-induced increases in BP metabolites were dose dependent, and they coincided with the magnitude of AHH induction The possibility that increased 7,8-diol synthesis could lead to increased synthesis of the ultimate BP carcinogen and prostate tumor induction is discussed. (30 Refs)

5. METABOLISM OF BENZO(A)PYRENE BY BRAIN MICROSOMES OF FETAL AND ADULT RATS AND MICE. INDUCTION BY 5,6-BENZOFLAVONE, COMPARISON WITH LIVER AND LUNG MICROSOMAL ACTIVITIES.

Rouet P, Alexandrov K, Markovits P, Frayssinet C, Dansette PM
Laboratoire de Physiopathologie cellulaire, Institut de Recherches Scientifiques sur le Cancer, BP No. 8, 94802 Villejuif Cedex, France
Carcinogenesis; 2(9):919-926 1981

Pregnant C57Bl/6 mice and WAG rats were injected ip with 5,6-benzoflavone (BF). On day 19 of gestation the animals were sacrificed, and fetal and maternal brain, lung, and liver microsome s were incubated with benzo(a)pyrene (BP). Liver microsomes of pregnant female mice were only slightly inducible compared with 10x and 4x control level induction of brain and lung microsomes. A 40x, 2x, and 16x control induction by BF was observed for fetal microsomes from the liver, brain, and lung, respectively. In rats, BP metabolism by brain microsomes was greater than that by lung microsomes. (44 Refs)

6. STUDIES IN THE METABOLISM OF CARCINOGENIC POLYCYCLIC HETEROAROMATIC COMPOUNDS. I. THE HEPATIC MICROSOMAL METABOLISM OF 7-METHYLBENZ[C]ACRIDINE.

Ireland CM, Holder GM, Ryan AJ
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Biochem Pharmacol; 30(19):2685-2690 1981

An enzyme assay for the metabolism of the carcinogenic aza-aromatic polycyclic compound 7-methylbenz[c]acridine has been developed using a modification of a radiochemical assay described for the polycyclic aromatic hydrocarbon benzo[a]pyrene by DePierre et al and Van Cantfort et al. When the activities of controlled microsomes and microsomes of phenobarbital-, 3-methylcholanthrene- and 7-methylbenz[c]acridine-pretreated animals were compared, strong similarities were displayed toward oxidation of benzo[a]pyrene and 7-methylbenz[c]acridine. These similarities were seen in turnover numbers, Michaelis constants, and inducibility of both enzyme systems. 7-Methylbenz[c]acridine afforded a Type I difference spectrum with 3-methylcholanthrene-pretreated microsomes. It is suggested that 7-methylbenz[c]acridine is oxidized by the same or a similar set of enzymes which is responsible for benzo[a]pyrene metabolism. (Author abstract) (39 Refs)

7. SLOWER STEP OF THE POLYCYCLIC AROMATIC HYDROCARBONS METABOLISM: KINETIC DATA FROM MICROSPECTROFLUOROMETRIC TECHNIQUES.

Salmon J-M, Thierry C, Serrou B, Viallet P
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Biomedicine; 34(4):102-107 1981

A microspectrofluorometer has been used for kinetic studies of the decrease of benzo(a)pyrene and benzo(k)fluoranthene fluorescence. This decrease is observed for single living cells: L cells and human peripheral blood monocytes, after their incubation with culture medium containing these compounds and washing the petri dish with fresh medium. The entire fluorescence spectra is recorded at given time intervals in order to watch at some eventual spectral modification. The fluorescence decrease is monoexponential and its parameters are computed with a program based on the least squares fit method. Such determination shows no difference between the calculated rate constants of metabolization for B(a)P and B(k)F and, as long as we consider L cells with a similar morphological shape, only statistical fluctuations of the rate constants of metabolism are observed. As compared, monocytes show faster kinetics of the decrease of the B(a)P intracellular fluorescence due to B(a)P metabolism, and also a more reached dispersion of the values of the rate constant than the one observed for L cells indicating some heterogeneity in the monocyte population of each donor. (Author abstract) (13 Refs)

BINDING TO CELLULAR MACROMOLECULES

8. METABOLISM OF BENZO[A]PYRENE BY HUMAN MAMMARY EPITHELIAL CELLS: TOXICITY AND DNA ADDUCT FORMATION.

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Proc Natl Acad Sci USA; 78(10):6251-6255 1981

Pure cultures of human breast epithelial cells and of fibroblastic cells in early passage provided the opportunity to ask whether either cell type had the capability for metabolizing chemical carcinogens and, if so, was the fate of the metabolic products compatible with chemical carcinogens being a factor in the initiation of breast cancer in women. For this purpose, cells were exposed to benzo[a]pyrene (BaP), and (i) the influence on growth potential and (ii) the extent, type, and persistence of adducts between the metabolites of BaP and DNA were measured. Compared with fibroblasts, inhibition of growth by epithelial cells was 50-100x more sensitive to BaP. Because of this differential sensitivity, epithelial cells were exposed to 4.0 uM BaP and fibroblasts were exposed to 4.0 uM BaP in the studies of DNA adduct formation. Separation by high-pressure liquid chromatography of adducts between (+-)-7,8-dihydroxy-9,10-expoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BaP diol epoxide) and nucleosides from purified DNA revealed that epithelial cells contained modified DNA within 6 hr after adding BaP. Adducts between the 7R anti stereoisomer of BaP diol epoxide and deoxyguanosine predominated at all times. syn BaP diol epoxide adducts with deoxyguanosine and what appeared to be BaP diol epoxide adducts with deoxycytidine were consistently present but at much lower frequency. All three types of BaP diol epoxide-DNA adducts persisted in epithelial cells for 72 hr in BaP-free medium. No adducts were detected in fibroblastic cultures until 96 hr after first exposure to BaP. At this time, the type and extent of BaP diol expoxide-DNA adduct formation was similar to that in epithelial cells exposed to one-tenth the dose of BaP. The type, extent, rate of formation, and persistence of the adducts in human breast epithelial cells was similar to that in cells transformable by exposure to BaP, an indication that they may be targets for chemically induced carcinogenesis. (Author abstract) (42 Refs)

9. NUCLEAR UPTAKE AND SUBSEQUENT NUCLEAR METABOLISM OF BENZO(A)PYRENE BINDING TO CYTOSOLIC PROTEINS.

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Cancer Res; 41(11,part1):4408-4414 1981

The binding of [3H]benzo(a)pyrene to proteins of rat liver cytosol, the nuclear uptake of cytosolic protein-bound [3H]benzo(a)pyrene, and the subsequent nuclear metabolism of the polycyclic hydrocarbon were investigated. The binding of [3H]benzo(a)pyrene to cytosol had a saturable high affinity component with a Kd of 2.54 nM and a capacity of 530 fmol/mg protein. Specific binding of [3H]benzo(a)pyrene to cytosol was also assayed using sucrose density gradient analysis. Nuclear uptake of protein-bound [3H]benzo(a)pyrene was demonstrated both directly and by sucrose density gradient analysis. The nuclear benzo(a)pyrene was readily converted to metabolites which were qualitatively and quantitatively no different from nuclear metabolites of exogenously (not protein associated) added [3H]benzo(a)pyrene. (Author abstract) (42 Refs)

10. THE EFFECT OF AN INDIVIDUAL'S BLOOD PRESSURE ON THE PERCENTAGE OF TOTAL 7,12-DIMETHYLBENZ[A]ANTHRACENE METABOLITES THAT BIND COVALENTLY TO DNA IN CULTURED RESTING LYMPHOCYTES.

Pero RW, Bryngelsson C, Ostlund C, Bryngelsson T, Norden A
Unit Community Care Sciences, S-240 10 Dalby, Sweden
Chem Biol Interact; 37(1):1-12 1981

A method for the quantitative analysis of the percent metabolism that results in covalent binding of 7,12-dimethylbenz[a]anthracene (DMBA) to DNA in viable resting human lymphocytes is described. The inter- and intra-experimental reproducibility as judged by the coefficient of variation and examined in the same individual over a 3-mo period was 31.4% and 13.9%, respectively. When the lymphocytes from 30 hypertensive individuals were exposed to 1 uM DMBA for 18 hr, the percent of total DMBA metabolites that bind DNA covalently was correlated to the blood pressures of the patients at the time of sampling ($r = 0.53$, p less than 0.005). No influences on the data from the type or duration of hypertensive drug treatment could be statistically determined for this sample of hypertensive patients. It was concluded that high blood pressure is a strong determinant in predisposing lymphocytes to increased genetic risk from induced DNA damage and that this relationship is not statistically affected by hypertensive drug therapy. (Author abstract) (33 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

11. THE MAJOR ADDUCTS OF CIS AND TRANS BENZO[A]PYRENE DIOL EPOXIDES CAUSE CHAIN TERMINATION DURING DNA SYNTHESIS IN VITRO.

Yamaura I, Rosenberg BH, Cavalieri LF
(c/o Cavalieri) Walker Lab., Sloan-Kettering Inst. Cancer Res., Rye, NY
Chem Biol Interact; 37(1):171-180 1981

We have studied DNA synthesis in vitro using as tempiate phiX174 DNA containing varying numbers of adducts formed by reaction with cis and trans benzo[a]pyrene (BP) diol-epoxides. The extent of DNA synthesis decreases with increasing numbers of adducts and there is a concomitant decrease in the size of the DNA products. Both decreases can be accounted for quantitatively by the assumption that synthesis terminates at every BP adduct. Since the majority of the adducts are located at the 2-amino group of guanine, we deduce that these adducts cause termination. The role of adducts at other sites is uncertain. The cis and trans BP diol-epoxides are indistinguishable with regard to chain termination, yet in vivo these isomers behave differently. These results suggest that chain determination alone is insufficient to account for the mutagenic effects of BP diol-epoxides. (Author abstract) (26 Refs)

12. INDUCTION OF ARYLHYDROCARBON HYDROXYLASE AND BLAST TRANSFORMATION IN HUMAN BLOOD LYMPHOCYTES.

Fukuhara M, Bohuon C, Gharbi N, Biret F, Boudene C
Inst. Public Health, Shirokanedai, Minoto-ku, Tokyo, 108, Japan
Biochem Biophys Res Commun; 102(1):8-14 1981

The induction of arylhydrocarbon hydroxylase (AHH) by benzo(a)pyrene and the degree of blast transformation were measured simultaneously in peripheral hyman lymphocytes. While the induction ratio (induced:basal level) of AHH and induction ratio per unit of blast transformation varied at different culture times and at different phytohemagglutinin (PHA) concentrations for a particular individual, the ratio of absolute induced AHH activity and unit of blast transformation yielded a consistent value at different culture times and different PHA concentrations for the individual. AHH inducibility may be a useful parameter for the study of cancer susceptibility if inducibility is expressed in this new manner. (23 Refs)

13. STIMULATION OF PROSTAGLANDIN PRODUCTION AND CHOLINE TURNOVER IN HELA CELLS BY LYNGBYATOXIN A AND DIHYDROTELEOCIDIN B.

Sakamoto H, Terada M, Fujiki H, Mori M, Nakayasu M, Sugimura T, Weinstein IB
Natl. Cancer Center Res. Inst., 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan
Biochem Biophys Res Commun; 102(1):100-107 1981

Release of prostaglandins (PG) and choline turnover were studied in HeLa cells treated with the indole alkaloids lyngbyatoxin A (LBT) and dihydroteleocidin B (DTC). Both LBT and DTC induced rapid increases in the release of PG and in choline turnover. The dose-response relationship with LBT and DTC was similar to that for the phorbol ester tumor promoter 12-O-tetradecanoyl-13-acetate. (22 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

14. MELATONIN INHIBITION AND PINEALECTOMY ENHANCEMENT OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS IN THE RAT.

Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B
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Cancer Res; 41(11,part1):4432-4436 1981

The effects of the pineal hormone, melatonin, and of pinealectomy on the incidence of mammary adenocarcinoma in Sprague-Dawley rats treated with 7,12-dimethylbenz(a)anthracene (DMBA) were investigated. Melatonin (2.5 mg/kg), begun on the same day as DMBA (15 mg) treatment and given daily in the afternoon for 90 days, significantly reduced the incidence of mammary tumors from 79% (control) to 20% (treated) (p less than 0.002). Rats pinealectomized at 20 days of age and treated with 7 mg of DMBA at 50 days of age had a lighter incidence of tumors (88%) compared to control animals (22%). Fifteen mg of DMBA, which resulted in a higher incidence of tumors, reduced the difference between pinealectomized and control animals. Melatonin only partially reversed the effects of pinealectomy, reducing the incidence from 87% (pinealectomy alone) to 63% (pinealectomy plus melatonin); however, the tumor incidence was still lower (27%) in nonpinealectomized, melatonin-treated animals. Assessment of plasma prolactin, luteinizing hormone, follicle-stimulating hormone, estradiol, and cortisol in DMBA-treated tumor-free and tumor-bearing animals revealed a significantly lower plasma prolactin concentration [27 +-5 (SE)ng/ml] in melatonin-treated animals as compared to vehicle-treated animals [65 +-8 ng/ml]. The concentration of plasma prolactin was less in melatonin-treated, pinealectomized rats (55 +-10 ng/ml) as compared to vehicle-treated, pinealectomized animals (101 +-13 ng/ml). Other hormones were not affected by melatonin treatment. These data support the hypothesis that melatonin inhibits the development of DMBA-induced mammary tumors in the rat while removal of the pineal gland stimulates development of such tumors. Additionally, these experiments provide evidence that these effects may be mediated by a suppression of plasma prolactin levels. (Author abstract) (28 Refs)

15. PRODUCTION OF OVARIAN TUMORS BY HORMONE ADMINISTRATION.

Araki S
Dept. Obstetrics and Gynecology, Kurume Univ. Sch. Medicine, Kurume 830, Japan
Kurume Med J; 28(1):35-43 1981

The influence of hormone administration on tumor production was studied in female Wistar rats implanted with chemical carcinogens (9,10-dimethyl-1,2-benzanthracene (DMBA), 20-methylcholanthrene, (MC), 3,4-benzpyrene (BP), or 4-nitroquinolin-N-oxide (NQO)). The hormones were an estriol preparation (EST), a progesterone preparation (PROG), a testosterone preparation (AND), a dexamethasone preparation (ACH), and human chorionic gonadotropin (HCG). The incidence of solid tumors was highest with DMBA, less with MC and lowest with BP and NQO. ACH and EST appeared to accelerate tumor growth: the incidence of solid tum ors at 20 wk was not significantly different, while at 40 wk it increased to 90% in the ACH group. Up to 20 wk in the hormone-treated groups, tumor incidence was low; however, the tumor incidence increased thereafter. The highest total incidence of cystic tumor was found in the EST group, compared to controls. The solid tumors included fibromas, sarcomas, and adenocarcinomas. In the AND, PROG, and EST groups, the tumors were either fibroadenomas or fibromas. In the HCG group fibroadenomas predominated. Sarcomas appeared in the 30th and 40th wk in the controls and the EST and PROG groups, respectively. The av wt of the tumors produced by ACH and EST was greater than the control, with the largest tumor in the EST group. (27 Refs)

16. THE BINDING OF 7,12-DIMETHYLBENZ[A]ANTHRACENE TO MAMMARY GLAND MACROMOLECULES IN THE HAMSTER: EFFECTS OF ENOVID FEEDING OR TRANSPLACENTAL EXPOSURE TO DIETHYLSTILBOESTROL.

Hertzog PJ, Lawson TA, Gingell R
Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England
Chem Biol Interact; 37(1):199-205 1981

The covalent binding of 7,12-[3H]dimethylbenz[a]anthracene ([3H]DMBA) to mammary gland macromolecules was studied in hamsters fed a contraceptive mixture, Enovid, those exposed transplacentally to diethylstilbestrol (DES), and controls. Compared with rats, hamsters are relatively resistant to DMBA mammary carcinogenesis, but susceptibility is increased by either of the above treatments with Enovid or DES. The amount of DMBA bound to DNA and protein was 4-5x greater than to RNA, but only DNA binding was persistent. Fifty-three percent of the DNA-bound DMBA was still present after 8 days. The amount of DMBA bound to hamster mammary DNA and its persistence was similar to that found in rats. Neither Enovid nor DES treatment altered the levels of binding to mammary macromolecules, nor their persistence. These results indicate that the species differences in the susceptibility to DMBA-induced mammary carcinogenesis in hamsters and rats, and modification of the former by hormones, is not due to differences in the activation of carcinogens. The role of hormones such as prolactin in the promotion phase of mammary gland carcinogenesis may explain these differences. (Author abstract) (18 Refs)

17. RELATION BETWEEN ADRENAL FUNCTION AND 7,12-DIMETHYLBENZ[A]-ANTHRACENE-INDUCED MAMMARY CANCER OF THE RAT.

Nakamura Y, Kodama M, Kodama T
Dept. Surgery, Inst. Balneotherapeutics, Kyushu Univ., 4546 Tsurumihara, Beppu 874, Japan
Gan; 72(5):679-683 1981

The excretions of urinary steroids were investigated in rats in the course of mammary carcinogenesis by 7,12-dimethylbenz[a]anthracene (DMBA). The carcinogen was fed to female Sprague-Dawley rats on days 50 and 64 after birth at a dose of 10 mg each. The excretion of urinary androgen, 11-deoxy-17-oxosteroid (11-DOOS), increased temporarily (at 80 days of age) in DMBA-treated rats as compared with non-treated controls. The excretion of adrenal corticosteroid, 17-deoxy-corticosteroid (17-DOCS), was lower than normal in the rats that failed to develop tumors within 200 days after receiving DMBA. The difference between the above non-responders and the tumor-developing responders (or the non-treated controls) was significant at 80 and 120 days of age, but not at 160 days of age. The final tumors wt at 160 days of age were also positively correlated to the excretion of 17-DOCS at 130 days

of age. It was indicated that the overall process of DMBA carcinogenesis could be promoted by the endogenous adrenocortical steroids. The possible mechanism underlying the production of mammary cancer is discussed in the light of the metabolic intimacy between DMBA and the adrenal steroids. (Author abstract) (17 Refs)

18. INHIBITION IN VIVO OF THE FORMATION OF ADDUCTS BETWEEN METABOLITES OF BENZO(A)PYRENE AND DNA BY BUTYLATED HYDROXYANISOLE.

Anderson MW, Boroujerdi M, Wilson AE
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Cancer Res; 41(11,part1):4309-4315 1981

Antioxidants have been shown to inhibit the carcinogenic effects of a variety of chemical carcinogens. For example, the phenolic antioxidant butylated hydroxyanisole (BHA) has been shown to be a potent inhibitor of benzo(a)pyrene (BP)-induced neoplasia in mouse lung and forestomach. The objective of the present study was to determine whether or not BHA, under conditions known to result in inhibition of BP-induced neoplasia, affects the formation of BP metabolite:DNA adducts. Following po administration of a carcinogenic dose of [3H]BP to A/HeJ mice, radioactivity was detected in the DNA of both lung and liver. Analysis of the deoxyribonucleosides by high-pressure liquid chromatography showed that the major adduct in both tissues cochromatographed with the (+-)-7beta, 8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was 10 to 15% of the BPDEI adduct in both lung and liver. Another adduct, possibly derived from BP phenol(s), was also detected in lung and was 10 to 20% of the BPDEI adduct. Treatment of animals with BHA decreased the amount of the BPDEI adduct in the lung and the liver approx 55 and 75%, respectively. The decrease in the amount of this adduct in the lung appears to correlate with the inhibition of pulmonary adenoma formation. Thus, BHA appears to inhibit BP-induced pulmonary adenoma formation by inhibiting the amount of the BPDE:DNA adducts formed in lung. Possible mechanisms by which BHA treatment inhibits the formation of BPDE:DNA adducts are discussed. (Author abstract) (44 Refs)

19. HUMAN SALIVA INACTIVATES MUTAGENICITY OF CARCINOGENS.

Nishioka H, Nishi K, Kyokane K
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 85(5):323-333 1981

Various carcinogens, suspected carcinogens, certain pyrolysates (beef, salmon, sodium glutamate, polypeptone), and cigarette smoke condensate (CSC) were incubated with human saliva from healthy subjects. Effects on mutagenicity were tested in a modified Ames test with Salmonella typhimurium strains TA 98 and TA 100. Metabolic activation for development of mutagenicity was required by aflatoxin B1, benzo(a)pyrene (BP), tryptophan pyrolysate-1 (Tr-P-1, isolated from boiled beef), the other pyrolysates, and CSC. No metabolic activation was required by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2; a nitrofuran used as a food additive during 1966-1975 in Japan), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl methanesulfonate (MMS), 4-nitroquinoline 1-oxide (4NQO) and quercetin. Saliva inactivated AF-2, MNNG, 4NQO, aflatoxin B1, BP, and Trp-P-1. Mutagenic activities of quercetin, pyrolysates of beef, salmon, and sodium glutamate, and CSC decreased to some extent; the activities of MMS and polypeptone pyrolysate were not affected. Boiled saliva inactivated AF-2 somewhat in TA 98 but not in TA 100 cultures. Complex mechanisms may be involved in the inactivation of mutagenicity of carcinogens by saliva. (22 Refs)

20. PROPHYLAXIS OF MAMMARY NEOPLASIA BY SELENIUM SUPPLEMENTATION IN THE INITIATION AND PROMOTION PHASES OF CHEMICAL CARCINOGENESIS.

Ip C
Dept. Breast Surgery, Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Res; 41(11,part1):4386-4390 1981

The present study was designed to determine the chemopreventive effect of dietary selenium supplementation in the initiation or promotion phase of 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in rats fed a high-fat diet. Control animals received 0.1 ppm of selenium (as sodium selenite), while experimental groups were supplemented with 5 ppm of selenium for various periods of time:-2 to +24,-2 to +2, +2 to +24, +2 to +12, +12 to +24, and-2 to +12. The time of 7,12-dimethylbenz[a]anthracene administration (50 days of age) was taken as Time 0, minus and plus signs represent the time in wk before and after 7,12-dimethylbenz[a]anthracene administration, respectively. The following conclusions were drawn from the results: (a) selenium can inhibit both the initiation and promotion phases of carcinogenesis; (b) a continuous intake of selenium is necessary to achieve max inhibition of tumorigenesis; (c) the inhibitory effect of selenium in the early promotion phase is probably reversible; and (d) the efficacy of selenium is attenuated when it is given long after carcinogenic injury. In addition, the present investigation also assessed the effectiveness of selenium in inhibiting the reappearance of mammary tumors that had regressed after ovariectomy. By supplementing tumor-bearing animals with 5 ppm of selenium in the diet immediately after endocrine ablation, it was found that tumors reappeared at a slower rate compared to the controls. The data suggested that selenium is not only effective in chemoprevention but can also be used as an adjuvant chemotherapeutic agent. (Author abstract) (35 Refs)

21. CHEMOPREVENTION OF MAMMARY TUMORIGENESIS BY A COMBINED REGIMEN OF SELENIUM AND VITAMIN A.

Ip C, Ip MM
Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263
Carcinogenesis; 2(9):915-918 1981

The effect of combined administration of selenium (Se) and retinyl acetate (RA) was studied in female Sprague-Dawley rats with 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors. DMBA was given intragastrically at 5 mg/wk for 3 wk. Starting 2 wk before initiation of DMBA administration, rats were fed a diet supplemented by Se (4 mg/kg) and/or RA (250 mg/kg) for 26 wk. Incidence of mammary gland tumors in rats exposed to DMBA alone was 90.0%, compared with 53.3% in rats treated with Se alone, 46.7% in rats treated with RA alone, 16.6% in rats treated with Se + RA for 28 wk, and 50.0% in rats treated with Se + RA-supplemented diet for only 18 wk. (32 Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

22. REDUCTION OF TUMORIGENICITY AND OF DIHYDRODIOL FORMATION BY FLUORINE SUBSTITUTION IN THE ANGULAR RINGS OF DIBENZO(A,I)PYRENE.

Hecht SS, LaVoie EJ, Bedenko V, Pingaro L, Katayama S, Hoffman D, Sardella DJ, Boger E, Lehr RE
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Res; 41(11,part1):4341-4345 1981

The tumor-initiating activities on mouse skin and in vitro metabolism of dibenzo(a,i)pyrene, 2-fluorodibenzo(a,i)pyrene, 3-fluorodibenzo(a,i)pyrene, and 2,10-difluorodibenzo(a,i)pyrene were compared. After an initiating dose of 500 ug, followed by promotion with tetradecanoylphorbol acetate, dibenzo(a,i)pyrene induced skin tumors in 85% of the mice and caused 5.8 skin tumors/mouse. The corresponding tumorigenic activities for the fluorinated compounds were: 2-fluorodibenzo(a,i)pyrene (85%; 1.7 tumors/mouse); 3-fluorodibenzo(a,i)pyrene (80%; 3.1 tumors/mouse); and 2,10-difluorodibenzo(a,i)pyrene (10%; 0.1 tumors/mouse). After an initiating dose of 100 ug, only dibenzo(a,i)pyrene showed significant tumor-initiating activity. 3,4-Dihydro-3,4-dihydroxydibenzo(a,i)pyrene was identified as a metabolite of dibenzo(a,i)pyrene formed by the 9000 x g supernatant from the livers of Aroclor 1254-pretreated rats. Another dihydrodiol was tentatively identified as 1,2-dihydro-1,2-dihydroxydibenzo(a,i)pyrene. The formation on these angular ring dihydrodiols was inhibited in the metabolism of 2-fluorodibenzo(a,i)pyrene and 3-fluorodibenzo(a,i)pyrene. Angular ring dihydrodiols were not detected in the metabolism of 2,10-difluorodibenzo(a,i)pyrene. These results suggest that an angular ring dihydrodiol, 3,4-dihydro-3,4-dihydroxydibenzo(a,i)pyrene, which can form a bay-region dihydrodiol epoxide, may be a proximate carcinogen of dibenzo(a,i)pyrene. (Author abstract) (25 Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

23. LARGE DIFFERENCES IN METABOLIC ACTIVATION AND INACTIVATION OF CHEMICALLY CLOSELY RELATED COMPOUNDS: EFFECTS OF PURE ENZYMES AND ENZYME INDUCTION ON THE MUTAGENICITY OF THE TWELVE MONOMETHYLATED BENZ[A]ANTHRACENES, 7,12-DIMETHYLBENZ[A]ANTHRACENE AND BENZ[A]ANTHRACENE IN THE AMES TEST.

Glatt H, Vogel K, Bentley P, Sims P, Oesch F
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Carcinogenesis; 2(9):813-821 1981

Benz[a]anthracene, 7,12-dimethylbenz[a]anthracene (DMBA), and 12 isomeric monomethylbenz[a]anthracenes were all activated by C3H mice liver preparations to mutagens in Salmonella typhimurium TA100. However, the modes and requirements of metabolic activation differed widely for the different compounds. Some compounds were readily activated by the postmitochondrial liver fraction (S-9 mix) from control mice, but others were activated only by S-9 mix from 3-methylcholanthrene- or phenobarbital-treated mice. All compounds were mutagenic when activated with S-9 mix from Aroclor 1254-treated animals. Purified microsomal epoxide hydrolase almost completely inhibited the mutagenicity of some compounds, but it potentiated that of others, particularly K-region methylbenz[a]anthracenes. Purified cytosolic dihydrodiol dehydrogenase decreased the mutagenicity of the strong carcinogens DMBA, 7-methylbenz[a]anthracene, and 12-methylbenz[a]anthracene by up to 41%. In contrast, the enzyme had relatively moderate effects on the other compounds. None of the activating systems gave a quantitative correlation between mutagenicity and carcinogenicity in whole animal tests. (67 Refs)

24. LUNG AND LIVER CELL-MEDIATED MUTAGENESIS SYSTEMS: SPECIFICITIES IN THE ACTIVATION OF CHEMICAL CARCINOGENS.

Langenbach R, Nesnow S, Tompa A, Gingell R, Kuszynski C
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Carcinogenesis; 2(9):851-858 1981

Carcinogens from three chemical classes were compared for mutagenicity in systems containing cocultivated adult Sprague Dawley rat hepatocytes or lung cells and Chinese hamster V79 cells. 7,12-dimethylbenz[a]anthracene (DMBA), 3-methylcholanthrene (MCA), and benzo[a]p yrene (BP) were mutagenic for V79 cells in the lung cell-mediated system. DMBA and MCA were less mutagenic in the liver system, and BP was negative in this system. Aflatoxin B1 was mutagenic in the liver cell system but was only weakly mutagenic in the lung cell system. Dimethylnitrosamine (DMN) was mutagenic only in the presence of liver cells. The metabolism of BP and DMN was investigated to gain insight into the causes of their organ specificity. For DMN, the lack of metabolic activation by rat lung cells apparently accounted for its lack of mutagenicity in the lung cell mediated system. BP was metabolized by both systems, but quantitative differences were observed in the metabolites detected. Lung cells produced primarily the 7,8-and 9,10-diols and little detectable 4,5-diol, whereas liver cells produced the 4,5-diol as the major metabolite. (38 Refs)

25. CHEMICAL CARCINOGENESIS IN THE RAT: COMMON MODE OF ACTION OF CARCINOGENS AT THE CHROMOSOME LEVEL.

Sugiyama T, Ueda N, Maeda S, Shiraishi N, Goto-Mimura K, Murao S, Chattopadhyay SC
Dept. Pathology, Kobe Univ. Sch. Medicine, Chuo-ku, Kobe, Japan 650
JNCI; 67(4):831-839 1981

The chromosomal distribution of chromosome aberrations (CA) and sister chromatid exchanges (SCE) induced by various chemical carcinogens such as 7,12-dimethylbenz[a]anthracene, 7,8,12-trimethylbenz[a]anthracene, 1-butyl-1-nitrosourea, urethan, 4-nitroquinoline 1-oxide, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, and the antineoplastic compound mitomycin C was studied with the use of noninbred Long-Evans male rat bone marrow cells in vivo and in vitro. The CA and SCE induced by these structurally different chemicals were distributed in similar pattern among and along chromosomes when the chemicals were given a short time (6 hr) before the metaphase cells were harvested. The specific distribution pattern of chemically induced CA and SCE along

chromosomes was attributed to the late DNA replication of the vulnerable chromosome regions. Conversely, x-ray-induced CA were distributed more randomly. Thus the different chemical carcinogens were shown to exert a similar genetic effect at the chromosome level. (Author abstract) (38 Refs)

26. CORRELATION BETWEEN PRENEOPLASTIC LESIONS IN RAT EMBRYO LUNG TREATED WITH B[A]P OR CSC IN ORGAN CULTURE AND TUMOUR PRODUCTION IN VIVO.

Michiels F, Duverger A, Chouroulinkov I
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Carcinogenesis; 2(9):885-896 1981

Three stage of preneoplastic alterations were observed in organ cultures of Wistar rat embryo lungs treated with benzo[a]pyrene (B[a]P) or cigarette smoke condensate (CSC). Stage I was characterized by hyperplasia, Stage II by adenopapillary structures and squamous metaplasia, and Stage III by the appearance of microadenomas. CSC induced more preneoplastic lesions than B[a]P and the lesions appeared at a faster rate. Susceptibility to the lung carcinogens varied with Wistar rat strain (WAG, Hollande, and WAF); only WAG explants developed Stage III lesions. Cells from the carcinogen-treated cultures were tumorigenic for isogeneic rats when inoculated ip. With B[a]P cells from the fifth subculture, tumor incidence was 100% after 12.8 wk. With control cells from the 24th subculture, tumor incidence was 66% after 25.2 wk. CSC cells did not induce tumors in 100% of the recipients before 23 passages. (44 Refs)

27. SISTER CHROMATID EXCHANGES (SCE) AND CHROMOSOMAL ABERRATIONS OF CULTURED CELLS OF MOUSE EMBRYO INDUCED BY IONIZING RADIATION AND CHEMICAL CARCINOGEN.

Piao C, Ge S, Gao F
Dept. Biological Effect of Radiation, Lab. Industrial Hygiene, Ministry of Public Health, Beijing, People's Republic of China
Acta Anat Sin; 12(2):220-224 1981

The effects of 60Co-gamma rays and benzopyrene in the induction of SCE and chromosome aberrations are described for cultured murine embryo cells. At a dose level of 300 rad, 60Co-gamma rays induced 1.3 and 24 times more SCE and chromosome aberrations respectively than the unirradiated controls, while a dose of 50 rad produced no difference. At a dose of 0.05 ug per ml of culture media, benzopyrene increased the frequency of SCE by about 1.8 times that of the control while no change in chromosome aberrations was observed. The significance of SCE and chromosome aberrations in the evaluation of carcinogens in discussed. (12 Refs) (In CHI)

28. RADIOSTERILIZATION OF RAT LIVER MICROSOME CONTAINING POSTMITOCHONDRIAL SUPERNATANT FOR MUTATION ASSAYS.

Barfknecht TR, Andon BM, Bishop WW, Thilly WG
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Environ Mutagen; 3(5):565-573 1981

Gamma-irradiation was tested as a method for sterilizing commercially prepared rat liver postmitochondrial supernatant (PMS) by adding a known number of radio-resistant Bacillus subtilis spores to PMS samples and determining a dose-response survival curve for the spores following gamma-irradiation. At the same time, uncontaminated samples of PMS were irradiated and assayed for their ability to metabolically activate automobile diesel soot (ADS) and soot-derived polycyclic aromatic hydrocarbons (PAH) and dimethylnitrosamine (DMN) to mutagens using the Salmonella typhimurium 8-azaguanine resistance forward mutation system. Based on the survival of B subtilis spores in frozen gamma-irradiated PMS, sterilization of PMS with a dose of 3 megarads (Mrad) was effective in reducing a contamination of 1,000 bacteria/ml or 10(6) bacteria/liter to 10(-3) bacteria/liter. At doses up to 6 Mrad at dose rates of 5 x 10(5) rads/hr there was little or no significant loss of the ability of irradiated PMS to metabolically activate ADS, and the diesel soot components, benzo(a)pyrene (BaP) and fluoranthene (FLA) to mutagens. At higher doses of gamma-irradiation, and at a dose rate of 3 x 10(6) rads/hr for 6 Mrad, a significant inacti[illegible]tion of the ability of PMS to activate BaP and FLA was noted. Thus, radiosterilized PMS can be used in mammalian cell mutation assay systems to detect PAH mutagenesis. (25 Refs)

29. ASSESSING CONSEQUENCES OF MARINE POLLUTION BY HYDROCARBONS USING SPONGES AS MODEL ORGANISMS.

Zahn RK, Zahn G, Muller WE, Kurelec B, Rijavec M, Batel R, Given R
Physiologisch-Chemisches Institut, Universat Mainz, D-6500 Mainz, W. Germany
Sci Total Environ; 20(2):147-169 1981

Mutagenic activity in marine sponges (mainly Tethya lyncurium from the Northern Adriatic and from Catalina Island off Los Angeles, California) due to polycyclic aromatic hydrocarbon (PAH) pollution was investigated using radiolabeled benzo(a)pyrene (BaP) as a model pollutant. Tethya was exposed to Diesel 2 oil pollution at a level of 1-6 ppm. The amount of label converted into any one of three polyamines changed significantly: in controls, 30% of the decarboxylate l ornithine molecules were found as amines, while under conditions of oil pollution 80% were found as amines. With the Ames test the pollutant level was shown to be 3+ (equivalent to 0.7 ppb BaP). Ornithine decarboxylase activity increased slightly during the first 16 days of exposure, but had increased 10x by day 24. An increase in DNA-dependent RNA polymerase activity was seen with exposure to 1 ppm Diesel 2 for 1-2 days; the increase was only significant 1-2 days after exposure. Mixed function oxidase (MFO) activity could not be detected. Significant coupling of BaP derivatives to protein, DNA, and RNA was observed; the largest amount disappeared in the protein fraction. When illumination of 5 x 10(4) lux was omitted, the coupling of BaP derivatives to the DNA fraction dropped to 1/74x the previous values or less. Increased binding of BaP derivatives to DNA in the presence of light was significant between 0.001 and 31 ppb. However, when activated microsomal fractions from fish that had been exposed to high levels of PAH were added, dark incorporation rose to significant levels which could be decreased by the addition of the MFO inhibitor 7,8-benzoflavone. Possible absence of DNA repair in the sponges is discussed. (52 Refs)

30. ANALYTICAL AND BIOLOGICAL ANALYSES OF TEST MATERIALS FROM THE SYNTHETIC FUEL TECHNOLOGIES. IV. STUDIES OF CHEMICAL STRUCTURE-MUTAGENIC ACTIVITY RELATIONSHIPS OF AROMATIC NITROGEN COMPOUNDS RELEVANT TO SYNFUELS.

Ho CH, Clark BR, Guerin MR, Barkenbus BD, Rao TK, Epler JL
Analytical Chemistry Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 85(5):335-345 1981

Mutagenicity of model compounds of aromatic nitrogen compound classes found in or possibly present in synfuel products was studied. Salmonella typhimurium tester strains TA1535, TA1537, TA1538, TA98, and TA100 were employed. Aromatic hydrocarbons with 1-4 rings produced no mutagenicity but 5-ring compounds (such as perylene and benzo(a)pyrene) exhibited significant mutagenicity. Most N-heterocyclics of from 1-4 rings produced no mutagenicity; 5-ring members like 1,2,7,8-dibenzacridine and 10-azobenzo(a)pyrene showed high activities while 2,2'-bipyridine and quinoline showed only slight activities. Presence of nitrogen may increase mutagenicity slightly but is not as important as the number of fused rings. Effects of amino and nitro groups substituted on the aromatic ring and of compounds containing 1 N atom in the ring and 1 amino substituent are also presented. Amino substituents have a significant effect in N-heterocyclic parent compounds. Multi-ring aromatic amines give a definite activity for a particular isomer whether the amino functional group is primary, secondary, or tertiary. Observed trends are discussed with reference to molecular structural features. (16 Refs)

31. INDUCTION OF GENE MUTATION IN AND CELL TRANSFORMATION OF MAMMALIAN CELLS BY MODIFIED PURINES: 2-AMINOPURINE AND 6-N-HYDROXYLAMINOPURINE.

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Environmental Carcinogenesis Group, Lab. Pulmonary Function, and Toxicology Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 27709
Proc Natl Acad Sci USA; 78(9,part2):5685-5689 1981

A classical mutagen in prokaryotic systems, 2-Aminopurine is inactive as a carcinogen in two animal species. To determine the basis for this discrepancy in the correlation between carcinogenesis and mutagenesis, the ability of 2-aminopurine to induce somatic mutation and neoplastic transformation concomitantly in the same cellular system was examined. 6-N-hydroxylaminopurine, a related modified purine that is a mutagen and a carcinogen, was also studied. 2-Aminopurine was a mutagen in Syrian hamster embryo cells, but its activity was very weak. The max induced mutation frequency with either of two mutational markers was only 7 x 10(-6) mutants per surviving cell. 2-Aminopurine also induced morphological transformation of the cells under the same conditions, but the frequency was only approx 0.04% per surviving colony. Neoplastic transformation of the cells after 2-aminopurine treatment was not observed in these experiments. These results indicate that 2-aminopurine is, at best, a weak transforming agent. The lack of carcinogenic activity in vivo with 2-aminopurine is consistent with these observations. In contrast to the results with 2-aminopurine, 6-N-hydroxylaminopurine was very effective mutagen in these cells (up to 10(-3) mutants per survivor) and induced morphological transformation of the cells in a dose-dependent manner. Furthermore, neoplastic transformation was induced by this nucleic acid base analog, the correlation of mutagenic activity with transforming ability of these two modified purines supports a relationship between mutagenesis and carcinogenesis. However, relative to other carcinogens, there is a quantitative difference in the ability of 6-N-hydroxylaminopurine to induce cell transformation and mutation. For example, in benzo[a]pyrene-treated cultures, the ratio of the frequency of induced morphological transformation to that of somatic mutation was approx 100, whereas for 6-N-hydroxylaminopurine-treated cultures, the ratio of transformation to mutation was only 3-12.5. This indicates that 6-N-hydroxylaminopurine is less potent than benzo[a]pyrene in inducing transformation when compared at equal mutagenic potency. This is consistent with our hypothesis that cell transformation, and possibly cancer, occurs predominantly as the result of a mutation at the chromosome level rather than a gene mutation. (Author abstract) (27 Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

32. A SIMPLE METHOD FOR THE DETERMINATION OF BENZO[A]PYRENE AND BENZO[K]FLUORANTHENE IN A MIXTURE.

Mohan Rao AM, Rajagopalan R, Vohra KG
Div. Radiological Protection, Bhabha Atomic Res. Centre, Bombay-400 085, India
Talanta; 28(8):607-609 1981

The noncarcinogen benzo[k]fluoranthene (BkF) has excitation and emission spectra identical to those of the carcinogen benzo[a]pyrene (BaP). A new method for determining interference due to BkF in thin-layer chromatography fractions of environmental samples to be analyzed for BaP is presented. The method is based on the quenching of BaP fluorescence by the addition of nitromethane and is applicable to BaP:BkF concentration ratios in the range 0.1-10.0. (4 Refs)

33. IMPROVED METHOD FOR THE QUANTITATIVE SEPARATION OF 3,4-BENZOPYRENE FROM FOOD.

Gertz C
Chemisches Untersuchungsamt der Stadt Hagen, Pappelstrasse 1, D-5800 Hagen, W. Germany
Z Lebensm Unters Forsch; 73(3):208-212 1981

A simple method was developed for the isolation of 3,4-benzo(a)pyrene from food. Without previous hydrolysis, extraction is performed with petroleum ether in the presence of a nonionogenic detergent. Benzo(a)pyrene and other polycyclic aromatic hydrocarbons are isolated by complexing them with caffeine in formic acid soln. The samples are analyzed by high-pressure liquid chromatography and thin-layer chromatography after clean-up. The benzo(a)pyrene levels found were 0.54 ug/kg in smoke pork, 1.36 ug/kg in hot-smoked ham, 1.53 ug/kg in mussels, 0.23 ug/kg in smoked mackerels, 0.51 ug/kg in baker's yeast, and 1.70 ug/kg in unrefined sunflower-seed oil. (28 Refs) (In GER)

34. EFFECTS OF PARTICULATE MATTER ON RATES OF MEMBRANE UPTAKE OF POLYNUCLEAR AROMATIC HYDROCARBONS.

Bevan DR, Riemer SC, Lakowicz JR
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J Toxicol Environ Health; 8(1/2):241-250 1981

In a continuation of earlier studies, the effects of particulates on the rates of uptake of four additional polyaromatic hydrocarbons (PAH) into model membranes, are presented. Particulates were prepared by suspending approx 1 g particles in 100 ml benzene and adding a benzene soln of the PAH at a ratio of 0.3 mg PAH/1 g particle, and evaporating benzene under a vacuum. Fluorescence emission spectra were recorded on an SLM Instruments photon-counting spectrofluorometer. Particles with adsorbed dibenzo(a,h)anthracene, benzo(g,h,i)perylene and 3-methylcholanthrene resulted in enhanced rates of membrane uptake of these PAH. Absorption to chrysotile and anthophyllite fibrous asbestos materials produced the greatest increase in membrane uptake compared to the microcrystalline preparations of PAH. Adsorption of dibenzo(c,g)carbazole to particles did not result in enhanced uptake, presumably as a result of high water solubility. The methods described permit characterization of particle-PAH mixtures relative to rate of PAH uptake into membranes. (28 Refs)

35. QUANTUM CHEMICAL STUDIES OF METHYL AND FLUORO ANALOGS OF CHRYSENE: METABOLIC ACTIVATION AND CORRELATION WITH CARCINOGENIC ACTIVITY.

Poulsen MT, Loew GH
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Cancer Biochem Biophys; 5(2):81-90 1981

Specific electronic properties related to metabolic transformation and adduct formation by DNA were calculated for a series of methyl, dimethyl and n-fluoro-5-methyl derivatives of chrysene with the aim of identifying molecular properties which could be used as reliable indicators of their relative carcinogenic behavior. Using the semiempirical all valence electron IEHT method, the bay region bonds of 5MC were found to have enhanced nucleophilic reactivity to epoxide formation relative to chrysene. In addition, in one of the nonequivalent bay regions, the 1, 2, 3, 4 region, the distal (1, 2) bond was found to be more reactive than the proximal (3, 4) bond. This reactivity pattern leads to an easily formed diol epoxide carbocation, the postulated ultimate carcinogen. By contrast, in the other (7, 8, 9, 10) bay region, the proximal (9, 10) bond is the more reactive, suggesting formation of the 'wrong,' ie, less stable diol epoxide carbocation. Consistent with earlier studies of other PAH, calculations by the INDO method of the ease of carbocation formation from a bay region diol epoxide yielded a set of values which gave a good correlation with carcinogenicity. (Author abstract) (29 Refs)

REVIEWS AND OTHER RELATED STUDIES

36. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.

Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

The roles of metals in enhancing or inhibiting carcinogenesis are reviewed. Conclusive evidence of the carcinogenicity of arsenic has not yet been found, although some studies suggest it. Arsenic may act as a cocarcinogen. Selenium seems to be weakly mutagenic in bacteria and some mammalian cell cultures. Antitumor properties have been reported in experimental animals. Zinc is necessary as a trace element in the diet and may have anticarcinogenic effects. Nickel is strongly carcinogenic in experimental animals and humans. Its effects may be counteracted by manganese. Lead has not been confirmed as a carcinogen, but its presence in the environment warrants high priority research particularly on its effects in combination with other compounds. Chromium has been related to lung, and possibly stomach, cancer in man. Cadmium contributes to prostatic cancer and Leydig cell tumors. These effects can apparently be counteracted by zinc treatments. Carcinogenesis by benzo[a]pyrene, nitrosamines, and asbestos appear to be promoted by some metallic dusts. Further studies in vitro and in appropriate animal systems are urged. (155 Refs)

37. OCCUPATIONAL CANCER: PROBLEMS AND TASKS OF MEDICAL PRACTICE.

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Z Aerztl Fortbild (Jena); 75(11/12):529-531 1981

The problems of occupational cancer and its prevention are discussed. Aside from ionizing radiation, asbestos and chemical substances are the most important carcinogenic factors in the working environment. The number of industrial chemicals with demonstrated or probable carcinogenic effect is only 30-40. They include aminodiphenyl, arsenic, asbestos, auramines, benzene, benzidine, technical chloromethylmethylether, chromium, 2,2-dichlorodiethyl sulfide, dichlorodimethylether, beta-naphthylamine, nickel, tars, mineral oils, and vinyl chloride. Aflatoxins, acrylonitrile, beryllium, polychlorinated biphenyls, cadmium, dimethylcarbonylchloride, dimethylsulfate, ethyl oxide, and carbon tetrachloride are probable carcinogens. Occupational exposure to asbestos was definitely established in 303/743 patients with malignant mesothelioma, and occupational exposure was probable in 70. The prevention of occupational cancer includes the limitation of the use and production of carcinogenic substance to the extent absolutely necessary technologically, ban on especially hazardous carcinogens, compliance with occupational safety measures and hygienic standards, and check-up and monitoring of workers who have ever been exposed to carcinogenic factors. (7 Refs) (In GER)

38. EPOXIDE HYDROLASE AND HEPATOCARCINOGENESIS.

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Trends Pharmacol Sci; 2(10):257-258 1981

The role of epoxide hydrolase (EH) in hepatocarcinogenesis is described. A search for markers associated with multistage

development of preneoplastic cells through focal and nodular stages to a hepatoma led to the discovery of the preneoplastic (PN) antigen, a microsomal antigen present in nodule and hepatoma cells. Through immunological studies EH was found to be a major PN antigen. A class of heterocyclics, including isoquinoline, norharman, and ellipticine, has been shown to stimulate microsomal EH. The requirement for a pyridinic nitrogen beta to a ring fusion suggests enzyme dictated specificity, while the pyridinic nitrogen suggests an electrophilic target. Reactive electrophiles, such as epoxides, have been found to regulate cell function and development. Perhaps endogenously formed epoxides play a role in liver adaptation during hepatocarcinogenesis. All hepatocarcinogen tests seem to cause an early (1-5 wk) induction of EH activity and microsomal content of the enzyme protein. One explanation for this early induction of EH is the production of increased amounts of an endogenous epoxide as an acute response. EH regulation during hepatocarcinogenesis is discussed with 2-acetylaminofluorene hepatocarcinogenesis as an example. (12 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.

Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.

Pershagen G
Dept. Environmental Hygiene, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.

Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.

Kazantzis G
IUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.

Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.

Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.

Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.

Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
In GER

9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.

Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.

Scoville B, White BG
Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.

Hardell L, Eriksson M
Onkologiska klinken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
In SWE

12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.

Edling C
Yrkesmedicinska klinken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.

Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.

Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

15. EPIDEMIOLOGY.

Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.

Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.

Schramm T, Ebeling K, Schwarz R, Herse E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
In GER

18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.

Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.

Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.

Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 103(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.

Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.

Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.

Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.

Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.

Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmanninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.

Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.

Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.

Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.

Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Polycyclic Aromatic Hydrocarbons and Related Compounds

SERIES CK07 No. 82/04 APRIL, 1982

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. MORTALITY STUDY OF CHEMICAL PLANTS IN THE KANAWHA VALLEY REGION OF WEST VIRGINIA (MEETING ABSTRACT).

Leet TL
No affiliation given
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The mortality experience of Union Carbide employees at three chemical plants in the Kanawha River Valley region of West Virginia will be evaluated in a study jointly conducted by the National Institute for Occupational Safety and Health (NIOSH) and the Union Carbide Corporation. These plants have produced many chemicals, including acrylonitrile, ethylene oxide, polycyclic aromatic hydrocarbons (PAH), vinyl resins, and pesticides. A company-sponsored proportionate mortality study based on 819 deaths known to Union Carbide found excess proportions of multiple myeloma and cancer of the kidney and CNS. Initial analyses will evaluate the validity of the apparent excesses as well as evaluate all other cause-specific mortality. Further analyses will test the epidemiologic association between 1) ethylene oxide exposure and leukemia and 2) PAH exposure in the coal hydrogenation process and cancer of the respiratory system, urogenital system, and skin. The study cohort includes approx 44,000 employees who were ever employed by Union Carbide in the Kanawha Valley between January 1, 1940 and December 31, 1978. Demographic and work history data have been coded, keypunched, and computerized for 10,000 active and 34,000 former employees. Vital status ascertainment has been initiated and death certificates are being collected for 6,800 (estimated) deceased employees. (no Refs)

2. THE RELATIONSHIP OF AIR POLLUTION TO LUNG CANCER IN CONTRA COSTA COUNTY (MEETING ABSTRACT).

Austin DF
Resource for Cancer Epidemiology Section, California Department of, Health Services Oakland, CA
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Contra Costa County, a nearly 2000 km2 area in the northeastern part of the San Francisco Bay Area, has a population of more than 600,000. It was one of 39 counties in the US which has been shown to have high mortality rates for specific cancer sites. The northern section of the county is heavily industrialized with five major petroleum refineries and many chemical plants. This project was designed to examine the relationship between air pollution in Contra Costa County and the incidence of cancer. Contra Costa County cancer incidence data for the period 1969-78 were available through the RCE's population-based registry, now a part of the NCI's SEER Program. Particulate air pollutants were collected and analyzed under an Environmental Protection Agency (EPA) grant. Hi-vol glass filters were collected every sixth day for one yr, from November, 1978, through October, 1979, at each of fifteen sampling stations. Particulate matter was analyzed for total suspended particulates (TSP), benzene-soluble organics (BSO), sulfates (S0(4)), nitrates (N0(3)), lead (Pb), selected polycyclic aromatic hydrocarbons (benzo(a)pyrene, benzo(gni)perlene, benzo(a)anthracene, chrysene and for some samples, coronene), and mutagenicity using the Ames test. Estimates of the av annual level of each of the measured pollutants are computed for the population centroids of each of the 115 census tracts in the county. The industrialized portion of the county was found to have an age-adjusted incidence rate of lung cancer which has increased over the 10 yr of study from about a 10% excess to about a 60% excess as compared to the non-industrial portion. The correlation of each air pollutant and of several combinations of the pollutants with lung cancer incidence is under examination. In addition, a case-control interview study of lung cancer, using population-based controls, is underway. Major factors under examination are smoking, occupation, diet and alcohol, air pollution and proximity to one of the 18 toxic waste dump sites, found only in the industrial portion of the county. (no Refs)

3. POLYCYCLIC AROMATIC HYDROCARBONS IN THE WORK ATMOSPHERE. DETERMINATION OF AREA-SPECIFIC CONCENTRATIONS AND JOB-SPECIFIC EXPOSURE IN A VERTICAL PIN SODERBERG ALUMINUM PLANT.

Bjorseth A, Bjorseth O, Fjeldstad PE
Central Inst. Industrial Res., Blindern, Oslo 3, Norway
Scand J Work Environ Health; 7(3):223-232 1981

Polycyclic aromatic hydrocarbons (PAH) were measured in air and in airborne particulates in a relatively new aluminum plant. Vertical pin Soderberg electrodes were used to obtain both stationary (area specific) and personal (job specific) samples. Day-to-day variation in the exposure of one worker and variations within the same job type were studied. Relative distribution of PAH, the fraction of PAH on particulates, and the ratio between particulate and gaseous PAH were determined. The PAH fraction of particulate matter was in the range 1-4% and the ratio between particulate and gaseous PAH in the potrooms varied from 0.2 to 1. A total of 167 personal samples were collected from 18 different job types during a 7-day sampling period in 1977. Spikepullers had the highest PAH exposure; the geometric mean of exposure exceeded 40 ug PAH/square meter in most job categories. Low exposures were found for foremen and tappers; levels of exposure for other workers were between those of spikepullers and of foremen and tappers. Observed values were measures of exposure given no use of protective aids; dust masks were extensively used, particularly for the more exposed jobs. Great variation was found in PAH exposure, even within the same job category. (16 Refs)

4. INVESTIGATION OF THE MUTAGENICITY OF PARTICULATE EXTRACTS OF CITY AIR FROM BERLIN.

Wullenweber M, Ketseridis G, Ruden H
Fachgebiet Hygiene, Technische Universitat Berlin, Amrumer Str. 32, 1000 Berlin 65, W. Germany
Haustechnik Bauphys Umwelttech; 102(5):263-265 1981

Particulate matter collected from the air over Berlin during a 2-mo period was analyzed for mutagenicity and content of polycyclic aromatic hydrocarbons (PAHs). Extracts of the particulates were mutagenic in Salmonella typhimurium strains TA98 and TA100. The degree of mutagenicity of the particulates collected at different times varied. Analysis of the PAH content of the samples revealed that some contained benz(a)pyrene. (7 Refs) (In GER)

5. ENVIRONMENTAL HEALTH DATABASE FOR NEW JERSEY (MEETING ABSTRACT).

Burke T
No affiliation given
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The Office of Cancer and Toxic Substances Research (OCTSR) of the New Jersey Department of Environmental Protection (NJDEP) was established in 1977 as a result of New Jersey's nation leading cancer mortality rates and growing concern about the presence of carcinogens and toxic substances in the environment. The long term goal is to establish a statewide profile of the distribution of toxics and carcinogens in the environment in order to aid in the regulatory and enforcement activities of NJDEP, develop new standards for control of these substances, and ultimately to better understand the relationship between these pollutants and human disease. The Comprehensive Environmental Health Database project being conducted in cooperation with the National Cancer Institute combines the extensive information on environmental toxics collected by NJDEP with disease mortality and morbidity data in a computer format to allow rapid staustical and geographic analysis and correlation. New Jersey's information on environmental toxics and carcinogens is perhaps the nation's most comprehensive. Examples of the data included in the project are: results of a statewide survey of industry to determine where over 200 toxic and carcinogenic compounds are being manufactured, used emitted and disposed; results of statewide chemical monitoring of ground, surface and drinking water supplies for organic compounds, heavy metals and pesticides; locations of over 300 abandoned hazardous waste disposal sites; results of extensive air monitoring for respirable particulates, volatile organics, heavy metals and polynuclear aromatic hydrocarbons; results of statewide Ames testing program on water and air samples. The presentation will include preliminary results of the statistical and geographic analysis of environmental data, and a discussion of the future application of the database in epidemiological research. (no Refs)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

6. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH
Sci Tech Aerosp Rep; 19(18):2533 1981

An environmental carcinogen, benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diol-epoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

7. CARCINOGEN SECRETION INTO THE DUODENUM AND PANCREATIC JUICE OF DOGS DURING FASTING AND POSTPRANDIALLY (MEETING ABSTRACT).

DiMagno EP, Demol P, Molenaar K, Go VL, Dozois RR
Gastroenterology Unit, Mayo Clinic, Rochester, MN, 55905
Newsletter Natl Pancreas Cancer Project; VI(2):19 1981

Fasting pancreaticobiliary secretions are cyclical, related to interdigestive motor activity and during peak rates approx 50% postprandial secretory responses. To determine if carcinogen secretion into pancreatic juice and the duodenum follows this pattern, four dogs were provided with three permanent indwelling duodenal catheters to perfuse 3H-polyethylene glycol (PEG), record duodenal pressures and collect duodenal samples for analysis of 14C, 3H, trypsin and bile acids. Two dogs were also provided with pancreaticocutaneous catheters to collect pancreatic juice. At the beginning of phase I, 50 uCi of 14C-1,2 benzanthracene was injected iv as a bolus. After three interdigestive motor-secretory cycles the dogs were fed 430 g of liver and samples obtained for four hr. We found: 1) 14C secretion (polar metabolites of benzanthracene by thin-layer chromatography and ultracentrifugation) into the duodenum during fasting was related to the interdigestive motor-secretory cycle. Thirty-five per cent of the injected dose was secreted during the interdigestive motor-secretory cycles (82% during phase II); 2) postprandially, 15% of 14C was secreted during 4 hr and most was secreted during the first hr (62%); and 3) a constant fraction (.03-.05%) of 14C recovered in duodenal samples was derived from pancreatic secretion. Thus, after a single brief exposure to a carcinogen, more than 50% of it (most in bile but small amounts in pancreatic juice) is secreted into the upper gastrointestinal tract as polar metabolites at variable rates in conjunction with the interdigestive motor-secretory complex and feeding. (no Refs)

8. THE METABOLISM OF BENZO(A)PYRENE IN TRANSFORMABLE AND NONTRANSFORMABLE C3H MOUSE FIBROBLAST CELL LINES.

Gehly EB
The University of Wisconsin, Madison, WI
Diss Abstr Int [B]; 42(3):913-B 1981

Incubation of benzo(a)pyrene (BaP) with intact C3H/10T1/2 cells for 48 hr resulted in the conversion of this carcinogen to organic-soluble derivatives, which cochromatographed with benzo(a)pyrene-7,8-dihydrodiol, benzo(a)pyrene-9,10-dihydrodiol, and 3-and 9-hydroxybenzo(a)pyrene, and to water-soluble derivatives. The metabolic activation of BaP was studied by testing a comprehensive series of 9 BaP metabolites for their ability to transform C3H/10T1/2 cells. Of all the derivatives examined, only (+/-) benzo(a)pyrene-7,8-dihydrodiol was as active as the parent hydrocarbon in the production of oncogenic transformation. In addition, the major DNA-binding species produced in BaP-treated C3H/10T1/2 cells was identified as benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide. These results strongly support current proposals that benzo(a)pyrene-7,8-dihydrodiol and benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide are the proximal and ultimate carcinogenic forms of BaP. The basis for cellular susceptibility to oncogenic transformation was investigated by comparing the metabolism of BaP by CVP3SC6 (CVP) cells, which are not responsive to BaP-induced transformation, and by C3H/10T1/2 cells. Although

CVP cell microsomes were not as active as C3H/10T1/2 cell microsomes in the metabolism of BaP, its metabolism by intact CVP and C3H/10T1/2 cells was quantitatively and qualitatively very similar. CVP cells could be transformed by BaP treatment plus exposure to the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). CVP cells treated with BaP plus TPA exhibited both morphological alterations and a loss of anchorage dependence. These studies emphasize that not only metabolic activation leading to DNA adduct formation and mutagenesis, but also the ability to express carcinogen-induced damage play an important role in determining cellular susceptibility to carcinogenesis. (no Refs)

9. THE INFLUENCE OF POLYCYCLIC AROMATIC HYDROCARBONS AS INDUCERS OF MONOOXYGENASES ON THE METABOLITE PROFILE OF BENZ(A)ANTHRACENE IN RAT LIVER MICROSOMES.

Jacob J, Grimmer G, Schmold A
Biochemisches Institut fur Umweltcarcinogene, Sieker Landstrasse 19, D-2070 Ahrensburg, W. Germany
Cancer Lett; 14(2):175-185 1981

Changes in metabolite profiles resulting from induction of monooxygenases by polycyclic aromatic hydrocarbons (PAH) in Wistar rats is reported. Benz(a)anthracene (BA) was used as substrate. Rat liver microsomes converted BA preferentially into 5,6-, 8,9-, and 10,11-trans-dihydrodiols. With control microsomes, approx 5x more 10,11-trans-dihydrodiol than 5,6-and 8,9-dihydrodiol was formed. All tested inducers increased the epoxidation at the 5,6-position and to a lesser extent at the 8,9-position. Oxidation at the 10,11-position, however, was decreased after almost all inducers. Treatment with more effective inducers resulted in an increased secondary metabolism, especially the formation of the bay-region dihydrodiol epoxide. While phenobarbital and the moderately-inducing PAH induced oxidation at the 5,6-and 8,9-positions, other compounds, especially the benzofluoranthenes, also induced oxidation at the 3,4-position. This reaction leads to formation of the ultimate carcinogen of BA, 3,4-dihydroxy-1,2-epoxy-1,2,3,4 tetrahydrobenz(a)anthracene. (35 Refs)

10. CHARACTERIZATION OF BENZOPYRENE HYDROXYLASE ENZYME ACTIVITY IN RAT PANCREAS (MEETING ABSTRACT).

Black O
Medical Research Service, Veterans Administration Medical Center, Augusta, GA, 30912
Newsletter Natl Pancreas Cancer Project; VI(2):11 1981

The increasing incidence of pancreatic cancer, the growing environmental pollution problems, and our increased knowledge of interactions of various exogenous factors such as diet, sex, etc, heightens the need for information on etiology of pancreatic cancer. There are presently several models of carcinogen-induced cancer. Establishment of the capability of tissue to form active intermediates is necessary to establish a relationship between exposure to carcinogens and subsequent tumorigenic response. The present studies were undertaken to characterize the pancreatic metabolic system, specifically that which metabolizes the ubiquitous carcinogen, benzopyrene (BP). We determined the Km and Vmax of the BP hydroxylase enzyme reaction in male Sprague Dawley rats pretreated with 20 mg/kg 3-methylcholanthrene (3MC), 75 mg/kg phenobarbital (PB), or solvent as control. Type of cytochrome involved was examined by measuring the reaction in the presence of 7,8-benzoflavone (BF), an inhibitor of the cytochrome P-448-related enzyme activity. The data indicated that the enzyme activity was induced by pretreatment with PB but not with 3MC. These pretreatment protocols resulted in changes both in Km and Vmax. Studies with BF suggested that pancreatic tissue contained only one hemoprotein and point out species differences between the rat and guinea pig. These studies confirm the pancreatic capability to metabolize procarcinogens and to further degrade carcinogenic metabolites, and strengthens the role of carcinogen exposure in the etiology of pancreatic cancer. (no Refs)

11. SPECIFICITY IN THE ACTIVATION AND INHIBITION BY FLAVONOIDS OF BENZO[A]PYRENE HYDROXYLATION BY CYTOCHROME P-450 ISOZYMES FROM RABBIT LIVER MICROSOMES.

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J Biol Chem; 256(21):10897-10901 1981

The effect of flavone and 7,8-benzoflavone on the metabolism of benzo[a]pyrene to fluorescent phenols by five cytochrome P-450 isozymes obtained from rabbit liver microsomes was determined. Benzo[a]pyrene metabolism was stimulated more than five-fold by the addition of 600 uM flavone to a reconstituted monooxygenase system consisting of NADPH, cytochrome P-450 reductase, dilauroylphosphatidylcholine, and cytochrome P-450LM3c or cytochrome P-450LM4. In contrast, an inhibitory effect of flavone on benzo[a]pyrene metabolism was observed when cytochrome P-450LM2, cytochrome P-450LM3b, or cytochrome P-450LM6 was used in the reconstituted system. 7,8-Benzoflavone (50-100 uM) stimulated benzo[a]pyrene metabolism by the reconstituted monooxygenase system about 10-fold when cytochrome P-450LM3c was used, but benzo[a]pyrene hydroxylation was strongly inhibited when 7,8-benzoflavone was added to the cytochrome P-450LM6-dependent system. Smaller effects of 7,8-benzoflavone were observed on the metabolism of benzo[a]pyrene by the cytochrome P-450LM2-, cytochrome P-450LM3b-, and cytochrome P-450LM4-dependent monooxygenase systems. These results demonstrate that the activating and inhibiting effects of flavone and 7,8-benzoflavone on benzo[a]pyrene metabolism depend on the type of cytochrome P-450 used in the reconstituted monooxygenase system. (Author abstract) (44 Refs)

12. EFFECTS OF CARCINOGENS, MUTAGENS, AND TERATOGENS ON NON-HUMAN SPECIES-AQUATIC ANIMALS (MEETING ABSTRACT).

Couch JA, Schoor WP
United States Environmental Protection Agency, Gulf Breeze, FL
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Aquatic systems and organisms are under both laboratory and field study in order to develop indicator, screening, and modeling capabilities for detection and evaluation of risks of carcinogens, mutagens, and teratogens. In the third yr of the program, several advances were made in the development of minnow (liver lesions via benzidine and aflatoxin exposures), rainbow trout (liver tumors via benzo(a)pyrene (B(a)P) exposures), and freshwater catfish (papillomatous-like lesions via chlorinated effluent exposures). A novel approach has shown that tiger salamanders may be good biochemical and histologic indicators of the presence of certain carcinogens (polycyclic

aromatic hydrocarbons-PAH's). The skin and liver tissues of the salamanders revealed induced enzyme activity following exposure to the PAH, perylene. Considerable field monitoring work on mollusks and carcinogenic PAH's along the coast of Oregon has revealed a positive correlation between prevalence of cellular proliferation disorders in shellfish and higher concentrations of certain PAH's in natural water. Emphasis in biochemistry for the last yr has been directed mostly toward the elucidation of the metabolisms of the mixed-function oxidases in marine organisms. From continuing work on the mullet (Mugil cephalus), we have found that benzo(a)pyrene is converted mainly to 3-hydroxybenzo(a)pyrene, 9-hydroxybenzo(a)pyrene and 4, 5-,7,8-,9,10-dihydroxydiols of B(a)P, in in vitro systems containing liver microsomes from Aroclor 1254-treated mullet. Other metabolites such as diones of B(a)P and probably tri- and tetraols have also been produced. We have also developed a procedure for the epoxide hydrolase enzyme system in order to determine the role of this enzyme on the metabolism of the polyaromatic hydrocarbons. These studies continue to reveal that fish have similar metabolic pathways to mammals for disposition of certain carcinogens. (no Refs)

BINDING TO CELLULAR MACROMOLECULES

13. BENZO(A)PYRENE METBOLISM AND COVALENT BINDING OF BENZO(A)PYRENE METABOLITES TO DNA.

Shen AL
University of Wisconsin, Madison, WI
Diss Abstr Int [B]; 42(3):880-B 1981

Benzo(a)pyrene metabolism and covalent binding of benzo(a)pyrene metabolites to DNA have been investigated in liver microsomes and hepatocytes prepared from 3-methylcholanthrene treated rats and in C3H/10T1/2/CL8 mouse embryo fibroblasts. In both hepatocytes and microsomal incubations, the major benzo(a)pyrene DNA adducts formed were adducts of anti- and syn- isomers of (-)-trans-7,8-dihydroxy-9,10-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (diol-epoxides) and of epoxide derivatives of benzo(a)pyrene-9-phenol (phenol-oxides). Diol-epoxide adducts predominated in hepatocytes while the reverse was found in microsomal incubations. C3H/10T1/2/CL8 fibroblasts metabolized benzo(a)pyrene to products which bound covalently to DNA. The major adducts were those arising from anti- and syn-benzo(a)pyrene diol-epoxides. (no Refs)

14. MODULATION OF THE COVALENT BINDING OF ARYL HYDROCARBON METABOLITES TO DNA IN VITRO AFTER TREATMENT OF RATS AND MICE WITH TRANS-STILBENE OXIDE.

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Carcinogenesis; 2(10):1049-1056 1981

Effects of trans-stilbene oxide (TSO) on in vitro microsome-mediated binding of benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) to purified DNA were investigated. Chromatograms of enzyme digests of DNA obtained from incubation of labeled BP metabolites with hepatic microsomes from TSO-treated Sprague-Dawley rats showed a decrease in peak H (nucleoside-bound 9-hydroxy-BP-4,5-oxide) without any significant modification of peaks E (nucleoside-bound syn- and anti-BP-7,8-diol- 9,10-epoxide) or G (nucleoside-bound BP-4,5-oxide). In vitro addition of the epoxide hydrolase inhibitor 1,1,1-trichloropropene 2,3-oxide (TCPO) produced 2.8-and 3.2-fold increases, respectively, in peaks G and H in microsomes from TSO-treated rats compared with those from controls. BP-metabolite-deoxyribonucleoside profiles obtained with microsomes from rats treated with BP (40 mg/kg) alone showed considerable covalent binding of BP-7,8-diol-9,10-epoxide and 9-hydroxy-BP-4,5-oxide; treatment with both BP and TSO (3 x 400 mg/kg) decreased binding to 45% and 25%, respectively. Microsomes from TSO-treated Swiss mice showed levels of BP-4,5-oxide and 9-hydroxy-BP-4,5-oxide binding that were 1.6-and 1.4-fold, respectively, greater than levels in microsomes from controls. The heights of peaks E, G, and H for C57BL/6 mice treated with TSO and BP were 53%, 60%, and 69% of the values obtained for mice treated with BP alone. After incubation of DNA with 3H-DMBA and BP- or TSO plus BP-treated rat liver microsomes, dual induction by BP and TSO was found to decrease DMBA metabolite binding to DNA, compared with induction by BP alone. The studies demonstrated the ability of TSO to increase the rate of oxidation at the K-region, due to induction of specific monooxygenases, and its ability to increase the rate of deactivation of epoxide intermediates by inducing microsomal epoxide hydrolase activity. The effects of TSO were similar for both substrates examined. (29 Refs)

15. THE DISTRIBUTION OF BENZO(A)PYRENE DNA ADDUCTS IN MAMMALIAN CHROMATIN.

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Nucleic Acids Res; 9(21):5533-5552 1981

This paper describes the distribution of DNA-lesions generated by the potent carcinogen benzo(a)pyrene (BP) or its ultimate metabolic derivative 7alpha,8beta,di-hydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDE) within mammalian chromatin using the enzymic probe micrococcal nuclease. We have shown that the progress of the nuclease on naked DNA is unaffected by the presence of the hydrocarbon lesion at moderate extents of digestion. Digestion of nuclei isolated from murine erythroleukemic cells immediately following BPDE treatment, and analysis of micrococcal nuclease resistant DNA by TCA precipitation, hydroxyapatite chromatography and gel electrophoresis demonstrates a non-random distribution of lesions. Approx 3x more binding occurs on the linker DNA regions between nucleosome cores than on the nucleosome core DNA itself. A similar result was obtained with BPDE treated primary mouse embryo cells; however nuclei isolated from these cells after prolonged treatment with BP (to allow metabolic activation) showed no such preferential binding. Post-treatment incubation of PBDE-treated c ells shows that this difference can be accounted for by the loss of preferential localization with time. (Author abstract) (33 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

16. HISTOLOGICAL AND ULTRASTRUCTURAL MORPHOLOGY OF 7,12 DIMETHYLBENZ(ALPHA)-ANTHRACENE CARCINOGENESIS IN HAMSTER CHEEK POUCH EPITHELIUM.

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Diagn Histopathol; 4(4):307-333 1981

Epithelial changes in 40 hamster cheeks during a 15 wk application of a 0.5% soln of 7, 12 dimethylbenz(alpha)anthracene were examined. During wk 2 and 3 of application an intense inflammatory reaction developed. By wk 8 irregular raised whitish patches with small pink or red nodules had appeared. By wk 10, the cheek pouches had taken on a whitish opalescent hue with nodules and plaques present to varying degrees. As tumors developed, they were often accompanied by hemorrhagic and necrotic areas on their surfaces. During carcinogenesis, epithelial thickness increased and parakeratinization was evident in the tumors. Intracellular spaces increased, whereas desmosomes decreased. Changes were observed in intracellular organelles. Increasing irregularity, discontinuity, and duplication of the lamina dura were seen in epithelial-connective tissue junctions. Lesions were classified as hyperplasia (epithelium 2x as thick as normal epithelium), dysplasia (epithelium showing several atypical features), and carcinoma (atypical epithelium with histological invasion of the adjacent connective tissue). (93 Refs)

17. QUANTITATIVE STUDIES OF HEMIDESMOSOMES DURING PROGRESSIVE DMBA CARCINOGENESIS IN HAMSTER CHEEK-POUCH MUCOSA.

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Br J Cancer; 44(3):440-450 1981

The present study was designed to establish whether there are changes in hemidesmosomal distribution during defined stages of chemical carcinogenesis in hamster cheek-pouch epithelium. 0.5% DMBA in liquid paraffin was applied thrice weekly to hamster pouches, and tissue samples were obtained at regular intervals and assigned to hyperplastic, dysplastic and carcinomatous groups on the basis of histological criteria. Untreated pouches served as controls. Following a strict sampling regime, electron micrographs were obtained from the epithelial-connective tissue junction and, using stereological intersection counting, the relative surface area of basal plasma membrane (BPM) occupied by hemidesmosomes was estimated. In normal epithelium 40% of the BPM is occupied by hemidesmosomes. During carcinogenesis, values decrease progressively and significantly to 35% in hyperplasia, 28% in dysplasia and 13% in carcinoma. A decrease in the rel ative area of hemidesmosomes would therefore appear to contribute to the increased motility of epithelial cells during connective-tissue invasion and cellular metastasis. (Author abstract) (47 Refs)

18. CYTOLOGIC FINDINGS IN CARCINOGEN-INDUCED CANINE LUNG TUMORS (MEETING ABSTRACT).

Yokota S, Pak HY, Teplitz RL, Benfield JR

City of Hope National Medical Center, Duarte, CA

Acta Cytol (Baltimore); 25(4):455 1981

Early detection of cancerous lesions of the lung is our ultimate goal and common interest. In order to better evaluate and understand the progression of changes in the development of lung neoplasia, a canine lung cancer animal model has been developed over the past six yr. This model was chosen for several reasons, including lending itself to the same procedural manipulations as used in humans, the feasibility and predictable induction of lung cancer at preselected sites and the rate natural development of lung neoplasms. To date, ten separate protocols using different carcinogens, doses and techniques have been employed. These include: benzo(a)pyrene (BP), nitrosomethyl-urea (NMU), dimethylbenzanthracene (DMBA), methylcholanthrene (MCA) and 91Ybeta radiation. These carcinogens have been introduced by intrabronchial and intrapulmonary sustained release implants of DMBA and 91Ybeta, respectively, and serial intrabronchial submucosal or topical application of aromatic hydrocarbons (BP, DMBA, MCA and NMU). Ten of 89 dogs enrolled in five of the ten protocols have developed lung neoplasms, all of which have been confirmed with histology. This paper describes the cytologic findings of the serial bronchial brushings and washings spanning preinduction of the carcinogens to the development of the lung neoplasms. (no Refs)

19. EARLY CHANGES OF HEMATOPOIETIC TISSUES IN MICE TREATED WITH INTRAVENOUS PULSE-DOSES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

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Acta Pathol Jpn; 31(5):799-814 1981

Repeated intravenous injections of 7,12-dimethylbenz(a)anthracene (DMBA), 4x weekly, induced several kinds of tumors in 26 mice (83.9%) out of 31 ddO mice, including 13 leukemias and 6 ovarian tumors. All leukemias were of lymphatic type, and 9 cases out of 13 leukemias were of thymus type. The thymus was involved by leukemic cells in 12 cases. All ovarian tumors were diagnosed as granulosa cell tumors histologically. During the treatment of DMBA, two types of changes in organs and blood were observed: one was a striking decrease of wt of organs or number of cells followed by prompt recovery as found in the spleen, red blood cells, and granulocytes in the peripheral blood; the other was moderate but long-standing decrease with little recovery as found in the thymus, ovaries, uterus, and lymphocytes in the peripheral blood . Unlike DMBA, the wt of the thymus was strikingly decreased by prednisolone, one of corticosteroids, whereas reactions of the spleen and the lymph nodes were not remarkable. Autoradiographical studies revealed a severe reduction followed by a marked rebound of labeling index in the red pulp of the spleen, but not in the white pulps of the spleen and cortex of the thymus. From these observations, it is concluded that a mild but long standing injury was noticed in the tissues which were the main sites of the tumorigenesis in mice by DMBA, and a severe but transient injury may not be related to induction of tumors in mice by DMBA. (Author abstract) (14 Refs)

20. BASE INSERTION AND DELETION MUTATIONS INDUCED IN AN ESCHERICHIA COLI PLASMID BY BENZO[A]PYRENE-7,8-DIHYDRODIOL-9,10-EPOXIDE.

Mizusawa H, Lee CH, Kakefuda T, McKenney K, Shimatake H, Rosenberg M
Lab. Molecular Carcinogenesis, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(11,part2):6817-6820 1981

Mutations induced by (+-)trans-benzo-[a]pyrene-7,8-dihydrodiol-9,10-epoxide (BaP-diol epoxide-1) were selected by using a recombinant plasmid vector system designed for the study of transcription termination signals. The plasmid contains a transcription terminator positioned between a promotor signal and the Escherichia coli galactokinase structural gene (galK). By selections for the expression of galK (ie, galK- to galK+), mutations are obtained in the terminator region that allow transcription from the promotor to read the galK gene. These mutations were characterized by direct DNA sequence of the terminator region. The DNA sequence changes caused by BaP-diol expoxide-1 were demonstrated for three different mutants. Two were found to be single-base-pair insertions of T-A into a cluster of consecutive T-A base pairs and the other change was a single-base-pair deletion of G-C from a cluster of consecutive G-C base pairs. (Author abstract) (30 Refs)

21. CYTOGENETIC CORRELATES OF LEUKEMOGENESIS IN RATS: SHORT- AND LONG-TERM EFFECTS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE ON CHROMOSOME BANDING.

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Diss Abstr Int [B]; 42(4):1313-B 1981

The hypothesis tested in this dissertation is that a correlation exists between the vulnerable chromosome sites of acute damage induced in marrow cell chromosomes by the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) and the pattern of altered chromosomes found in the marrow cells of rats made leukemic by DMBA. Chromosome banding techniques which permit identification of the individual rat chromosomes were instituted for this study. The location of chromosome alterations can be specified with regard to bands, sub-bands and banding regions. In short-term (acute) experiments, DMBA induced in high incidence of chromosome breaks. On banded chromosomes, breaks were distinguished from light bands only when chromosomes were stained sufficiently dark or when banding on sister chromatids was not aligned. Some chromatid breaks appeared to be intercalary deletions; other breaks appear to be without deletion (loss of substance) but with the chromosome axis malaligned. Breaks in the terminal regions were common. The chromatid breaks induced by DMBA were shown to be nonrandom and were highest in chromosome regions 2q2, 6q2, 1p1, 1q3, 5q3, 4q2, 6q1, and 12p1. These data indicated that the damage induced by DMBA is nonrandom, some chromosome regions showed greater vulnerability to damage by DMBA. Markers chromosomes in leukemic marrow cells involved t(1;2); t(1;4); t(1;6); t(1;7); t(1;9), with each associated with one normal chromosome 1 (monosomy 1p) and two normal number 2, No 4, No 6, No 7, or No 9 chromosomes. Trisomy No 2, 16 and 20 and monosomy No 5, 6, 10 and 18 occurred in leukemic rats but not in control rats. The data presented suggest that leukemogenesis by DMBA requires specific changes at multiple (ie, combination) chromosome sites. The number of these postulated critical sites required in the combination is not known, but our data identify the following morphologic regions as likely to contain these sites: 1q2, q3; the pericentromeric region of No 2 chromosome; 4q4; 5q3; 6q1; 6q2; 9q3; 11p; 12p; and 12q1. (no Refs)

22. RAPID INDUCTION OF GAMMA-GLUTAMYL TRANSPEPTIDASE-RICH INTRAEPITHELIAL CLONES IN 7,12-DIMETHYLBENZ(A)ANTHRACENE-TREATED HAMSTER BUCCAL POUCH.

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Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, Boston, MA, 02115
Cancer Res; 42(1):285-291 1982

Individual gamma-glutamyl transpeptidase (GGT)-stained cells and cell doublets were rapidly induced in the epithelium of hamster buccal pouch treated with biweekly topical applications of 0.5% 7,12-dimethylbenz(a)anthracene (DMBA) in mineral oil. The cells were detected histochemically in whole mounts of pouch epithelium harvested as early as 3 days after the first application of this carcinogen. During 3 consecutive wk of DMBA treatment, progressively larger GGT-stained epithelial cell populations (plaques) up to 0.5 mm in diameter were encountered. Similar GGT-stained lesions were not detected in whole mounts of untreated epithelium and were rarely seen in GGT-stained whole mounts prepared from mineral oil-treated pouch epithelium. In an experiment designed to assess the stability of the GGT-staining pattern, very few plaques could be detected 12 wk after a 3-wk regimen of six DMBA applications. However, data are presented suggesting that a brief series of three DMBA applications reinduced GGT histochemical activity in occult intraepithelial plaques, which had lost enzyme activity but had persisted over an 11-wk treatment-free interval. The clonal nature of the GGT-stained plaques and their apparent ability to persist in an occult form for several wk or mo lend further support to the hypothesis that these carcinogen-altered cell populations may be potential precursors for the development of squamous epithelial neoplasia. (Author abstract) (40 Refs)

23. IN VITRO REACTIVITY OF ALVEOLAR MACROPHAGES AND RED BLOOD CELLS WITH ASBESTOS FIBERS TREATED WITH OXALIC ACID, SULFUR DIOXIDE AND BENZO-3,4-PYRENE.

Jaurand MC, Magne L, Boulmier JL, Bignon J
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Toxicology; 21(4):323-342 1981

Effects on in vitro reactivity with alveolar macrophages and RBCs as a result of adsorption of sulfur dioxide (SO2) and benzo(a)pyrene (BP) onto asbestos fibers was investigated. Two samples of quartz and glass, and nemalite fibers were tested as controls. Untreated chrysotile fibers were highly hemolytic; untreated amphibole fibers were not. After treatment with oxalic acid, the effects of leached amosite and leached crocodilite were greater than those of untreated fibers on both RBC and alveolar macrophages (AM). Treatment of chrysotile with oxalic acid greatly modified its activity, inducing a 5x reduction in hemolysis and a slight decrease in lactate dehydrogenase (LDH) level released from AM after 20 hr incubation compared with controls. Treatment with SO2 had little effect on the capacity of leached or unleached fibers to cause hemolysis in RBC or on the release of enzymes from AM. BP-treated leached chrysotile fibers decreased the AM release of beta-galactose from 13% to 8% and that of LDH from 20% to 5%. (34 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

24. TUMOR PROMOTION STUDIES IN RAT TRACHEAL EPITHELIUM (MEETING ABSTRACT).

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National Institute of Environmental Health Sciences, Research Triangle Park, NC
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Tracheal epithelium of the Fisher 344 rat is histologically very similar to that of the human bronchus. Also, carcinomas of tracheal origin in F-344 rats are similar in morphology to human bronchogenic carcinomas. Two model systems exist to study tumor promotion in rat tracheal epithelium. The first is a heterotopic tracheal transplant system in which rat tracheas are implanted sc on the backs of isogenic recipients. The epithelium was then topically exposed to pellets containing 7,12-dimethyl-benz(a)anthracene, DMBA, used as the initiating agent, followed by pellets containing the phorbol ester 12-O-tetradecanoylphorbol-13-acetate, TPA, the promoting agent. After 98 wk, 3-4 fold increase in the percentage of trachea s having malignant tumors was seen in tracheal transplants receiving both DMBA and TPA compared to DMBA alone. Exposure of the tracheal grafts to TPA alone resulted in epithclial hyperplasia and inflammation, but no dysplastic lesions. The second system is an organ culture-cell culture system in which small pieces of trachea are grown in organ culture, then epithelial cells are grown from these pieces as primary cell cultures. The organ cultures were exposed to the direct alkylating agent, N-methyl-N'-nitro-N-nitrosoguanidine, MNNG, used as the initiator, then multiple short exposures to TPA are used to promote. Primary cell cultures and cell lines were then established from these explants. After 52 wk, a five-fold increase in the percentage of explants producing tumorigenic cell lines was observed when MNNG + TPA exposed explants were compared to MNNG exposed explants. Tracheal explants exposed to TPA alone produced many cell lines but none tested were tumorigenic. These two systems provide a means to study tumor promotion in respiratory epithelium. The evidence more importantly suggests that airborne promoting substances may play a key role in the development of bronchogenic carcinoma. (no Refs)

25. TUMOR PROMOTERS AND COCARCINOGENS IN TOBACCO CARCINOGENESIS (MEETING ABSTRACT).

Hoffmann D, Hecht SS, Wynder EL
American Health Foundation, Valhalla, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Cigarette smoke induces carcinoma of the larynx in Syrian golden hamsters and is active as a tumor promoter in hamsters pretreated with a low dose of a polynuclear aromatic hydrocarbon, nitrosamine, or nitrosamide. These tumorigenic effects are only observed with total smoke, but not with the gas phase alone. This demonstrates that the tumorigenic agents reside primarily in the particulate phase. According to fractionation experiments, a number of four- and five- ring aromatic hydrocarbons serve as the major tumor initiators in tobacco smoke. Tumor promoters reside primarily in weakly polaric neutral subfactions and in the weakly acidic portion of the particulate matter and include certain unsaturated hydrocarbons and phenolic compounds. Cocarcinogenic activity is a characteristic feature of tobacco smoke and its particulates. Among the cocarcinogens formed during combustion are catechols and certain non-tumorigenic aromatic hydrocarbons and terpenes. Nicotine may also serve as a cocarcinogen as is indicated by preliminary data. The presentation will discuss the action of tumor promoters and cocarcinogens in tobacco carcinogenesis, the precursors for tobacco smoke promoters and cocarcinogens, and methods for their reduction in smoke. (no Refs)

26. POTENT ENVIRONMENTAL TUMOR PROMOTERS FOUND IN STREPTOMYCES AND BLUE-GREEN ALGA (MEETING ABSTRACT).

Fujiki H, Sugimura T, Moore RE
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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

It is well known that tumor promoters induce ornithine decarboxylase (ODC) activity in mouse skin and that this induction can be inhibited by the application of 13-cis-retinoic acid. These two properties of tumor promoters were utilized for screening new tumor promoters in our environment. Two new classes of tumor promoters are presented: 1) Indole alkaloid (teleocidin and lyngbyatoxin); and 2) Polyacetate (aplysiatoxin and debromoaplysiatoxin). Teleocidin from Streptomyces and lyngbyatoxin, from the blue-green alga, Lyngbya majuscula, were able to induce ODC activity in mouse skin and showed various biological activities similar to those of tetradecanoyl phorbol acetate (TPA). Teleocidin and lyngbyatoxin are indole alkaloids. Their tumor promoting activities became apparent in the mouse skin through a two-stage carcinogenicity test. The tumor incidence of the group treated with dimethylbenzanthracene (DMBA) plus teleocidin was 100% at wk 30, which was similar to that of the group given DMBA and TPA. The in vivo carcinogenicity test with lyngbyatoxin is still underway. The tumor incidence of the group treated with DMBA plus lyngbyatoxin is 80% at wk 21. A second new class of tumor promoter is polyacetate. Aplysiatoxin and debromoplysiatoxin were isolated from another variety of blue-green alga. Aplysiatoxin and debromoaplysiatoxin induced ODC to the same degree of potency. However, aplysiatoxin induced various membrane effects, such as adhesion of cells and turnover of phospholipid with a similar concentration of TPA, teleocidin and lyngbyatoxin. On the other hand, debromoaplysiatoxin required an amount almost 100 x greater to achieve the same effects. (no Refs)

27. TISSUE DAMAGE AND NUTRITIONAL FACTORS IN EXPERIMENTAL RESPIRATORY TRACT (CO-) CARCINOGENESIS (MEETING ABSTRACT).

Kroes R, Reuzel PG, Feron VJ, Spit BJ, Beems RB
Institute CIVO-Toxicology and Nutrition TNA, The Netherlands
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Co-factors involved in respiratory tract carcinogenesis are studied in Syrian golden hamsters using benzo(a)pyrene as the carcinogenic agent. These factors include severe tissue damage induced by electro-coagulation, glass fibers administered by intratracheal instillation, acetaldehyde as irritant vapor, food restriction, and nutrients such as vitamin A and saturated and unsaturated fats. A combined exposure to four different major gaseous cigarette smoke components viz methyl nitrite and i soprene and one solid cigarette smoke component, nor-harman are examined in short- and long-term inhalation studies. An in-

teresting finding was the carcinogenicity of acetaldehyde, of which the possible mechanism is briefly discussed. Another conspicuous observation was the substantial increase in number and size of lipid droplets in alveolar macrophages of hamsters fed a high vitamin A diet. (no Refs)

28. PROMOTION OF CARCINOMAS BY REPEATED ABRASION IN INITIATED SKIN OF MICE.

Argyris TS, Slaga TJ
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Cancer Res; 41(12):5193-5195 1981

Repeated abrasion of the skin of Sencar mice initiated with 100 nmol of dimethylbenzanthracene resulted in the appearance of carcinomas in addition to papillomas. These results strongly support the argument that repeated epidermal regeneration is a sufficient stimulus for the promotion of both benign and malignant neoplasms in the skin of mice. (Author abstract) (5 Refs)

29. INFLUENCE OF AGE AND PARITY ON THE SUSCEPTIBILITY OF RAT MAMMARY GLAND EPITHELIAL CELLS IN PRIMARY CULTURES TO 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Russo J, Wilgus G, Tait L, Russo IH
Experimental Pathology Lab., Dept. Biology, Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI, 48201
In Vitro; 17(10):877-884 1981

Mammary gland epithelial cells from rats of different ages or with different reproductive histories vary in their proliferative properties and susceptibility to dimethylbenz(a)anthracene (DMBA) carcinogenesis in vivo. The present study was carried out to determine whether these differences are maintained under in vitro conditions. Primary cultures of mammary gland epithelial cells of young virgin, old virgin, and parous rats were treated with various doses of DMBA. Growth rates, DNA synthesis, and dose-response curves were determined; the toxicity of DMBA was measured by its effect on cell growth. Cell morphology was studied by transmission and scanning electron microscopy. Epithelial cells from the mammary gland of young virgin rats adapted rapidly to the culture conditions, behaving as if the cells were in the logarithmic phase of growth prior to plating. Mammary gland epithelial cells from old virgin and parous rats required a lag period prior to cell growth during which the proliferating cells adapted to the culture conditions. Cells from each group had comparable doubiing times, and DNA synthesis peaked approx 1 day after initiation of growth in culture. The numbers of proliferating cells decreased with increasing age and parity of the donor. Mammary gland epithelial cells of young virgin rats were more susceptible to both low and high doses of DMBA than those of old virgin and parous rats when the carcinogen was added either 24 hr after plating or at the peak of DNA synthesis. These results indicate that age and parity influence the proliferativ e status of the cells and their susceptibility to DMBA in vitro, simulating in that way the in vivo situation. (Author abstract) (35 Refs)

30. MAMMARY-TUMOUR INCIDENCE IN SPRAGUE-DAWLEY RATS TREATED WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE: EFFECT OF PREGNANCY AND LACK OF EFFECT OF UNILATERAL LACTATION.

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Br J Cancer; 44(3):451-455 1981

Mammary teat removal (thelectomy) was performed unilaterally in female Sprague-Dawley rats at 35 days of age. They were given 7,12-dimethylbenz(a)anthracene (DMBA) when aged either 55 days or 79 days. One third were unmated; one third were mated 1 wk and one third mated more than 3 wk after DMBA administration. Animals were killed when tumor-positive or after 1 yr, when mammary lesions had developed in 99% of rats. The mean latent period for adenocarcinomas was 18.9 +-2.0 wk. Benign mammary tumors, mainly secretory adenomas, developed significantly later (39.2 +-1.7 wk). The rapid unilateral involution of the thelectomized glands at parturition had no effect on the localization of either adenocarcinomas or benign mammary tumors. Pregnancy and delayed DMBA administration markedly reduced the incidence of adenocarcinomas; lactation had no significant effect. In a separate experiment, precocious puberty induced with pregnant-mare-serum gonadotrophin in 30-day-old female Sprague-Dawley rats enabled their first pregnancy and lactation to be completed by 80 days of age. Parity before carcinogen administration significantly delayed the development of adenocarcinomas. (Author abstract) (19 Refs)

31. NATURAL KILLER CELL ACTIVITY AND TUMOR SUSCEPTIBILITY IN FEMALE MICE TREATED NEONATALLY WITH DIETHYLSTILBESTROL.

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Cancer Res; 41(12):5134-5140 1981

Female NMRI or AKR/J mice were given daily sc injections of 5 ug diethylstilbestrol (DES) in 0.025 ml olive oil, or of olive oil only, for the first 5 days after birth. At the age of 6 to 7 wk, both DES-treated females and control females were killed, and the cytotoxic activity of the spleen cells against standard natural killer cell target YAC-1 cells as well as the natural killer cell-sensitive I-522 cells and relatively insensitive I-51 AKR lymphomas was tested. The cytotoxic activity against I-51 cells was similar for DES-treated and control females while the DES-treated females had only about one-half the cytotoxic activity to I-522 and YAC-1 cells as did controls. Control females eliminated radioactivity derived from 125-I-labeled YAC-1 and I-522 target cells injected iv faster than did DES-treated females, while the results were similar for both animal groups when using 1-51 cells. The cumulative death incidence was higher for DES-treated females than for control females after inoculation with low numbers of I-522 cells but similar for both groups when using I-51 cells. Finally, the incidence of females developing methylcholanthrene-induced sarcomas, using a single low-dose injection (10 or 20 ug), was higher among DES-injected animals than among controls. Taken together, the results indicate that female mice treated neonatally with DES have a functionally defective natural killer cell population, resulting in increased tumor susceptibility. (Author abstract) (50 Refs)

32. EFFECT OF HERPES INFECTION ON INDUCTION OF CERVICAL CANCER BY METHYLCHOLANTHRENE IN MICE (MEETING ABSTRACT).

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Obstetrics and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia. Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

It is unknown whether herpes simplex virus type 2 (HSV-2) is one of the possible etiologic agents of human cervical cancer or not. The present study was performed to evaluate any possible carcinogenic activity of HSV-2 in the genital tract of the female mouse. The 'string method' of methylcholanthrene (MC) was used to induce carcinoma of the uterine cervix in mice. Two kinds of experiments were designed as follows: (1) Impregnation of MC threads was first carried out, and 7 wk later these were removed and half of the mice were infected with HSV-2 in the genital tract, while the other half were not. One, 2 and 3 mo later, several mice from both groups were sacrificed and the histological changes in the squamous and columnar epithelium were examined. A synergistic effect of MC and HSV-2 on the columnar areas was not observed, whereas this effect was clearly demonstrated on the squamous areas, especially in the specimens prepared from the mice at 3 mo after HSV infection. (2) Mice were first infected and 10 days later MC treatment was carried out. Three experimental groups of HSV(+)MC(+), HSV(+)MC(-), and HSV(-)MC(+) treated mice studied as controls. Four mo after MC treatment, all mice were sacrificed and examined. In this experiment, the appearance of atypia III (corresponding to carcinoma-in situ in the human) and invasive lesions of the cervix were frequently detected in the group of HSV(+)MC(+). From these investigations, it is postulated that herpetic infection may enhance induction of cervical cancer. (no Refs)

33. INHIBITORY EFFECT OF HUMAN URINARY EXTRACT ON THE GROWTH OF DMBA-INDUCED MAMMARY TUMORS IN HOLTZMAN RAT.

Sarkar S, Shah PN, Bagli NP
Cancer Res. Inst., Bombay 400 012, India
Neoplasma; 28(4):457-461 1981

The effect of a crude protein fraction from human urine having gonadotropin inhi bitory activity (CGIM) was observed on the growth of 7,12-dimethylbenz(a)anthracene induced mammary tumors in the Holtzman rat. Results show that while in 12 out of 13 tumors, tumor growth was retarded/regressed following 2-4 wk of CGIM treatment, tumor growth in control rats was unabated. However, no positive correlation with hormone dependency and tumor regression could be established. Further, this crude anti LH material was found to be non-toxic to tumor cells in vitro. (Author abstract) (11 Refs)

34. IMIDAZOLE DERIVATIVES AS INHIBITORS OF CYTOCHROME P-450-DEPENDENT OXIDATION AND ACTIVATORS OF EPOXIDE HYDROLASE IN HEPATIC MICROSOMES FROM A MARINE FISH.

Little PJ, James MO, Bend JR, Ryan AJ
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Biochem Pharmacol; 30(20):2876-2880 1981

Binding of 4(5)-phenylimidazole, benzimidazole, and naptho(2,3,4',5')-imidazole to cytochrome P-450 in sheepshead hepatic microsomes was examined; effects of these compounds on benzo[a]pyrene metabolism in control and induced microsomes are described. (39 Refs)

35. THE EFFECT OF 3-METHYLCHOLANTHRENE AND 3-METHYLCHOLANTHRENE PLUS PIRACETAM ON THE GAMMA-AMINOBUTYRIC ACID (GABA) CONTENT OF SEVERAL CEREBRAL REGIONS.

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J Cancer Res Clin Oncol; 101(3):339-343 1981

The effects of piracetam (PA) on elevation of gamma-aminobutyric acid (GABA) in cerebral regions of female Wistar rats by 3-methylcholanthrene (3-MC) were studied. Groups of rats were treated variously with PA (100 mg/kg body wt/administration, delivered by stomach tube), 3-MC (6 mg/kg body wt/administration, sc), or combinations of both. Total doses and timing of treatments varied. Treatment with 3-MC produced a rapid elevation of GABA in the hypothalamus and a more delayed elevation in the hippocampus. Walker's carcinoma also produced elevated GABA in these regions. PA alone did not affect GABA levels. Short-term PA treatment did not reduce GABA levels elevated by 3-MC, but chronic PA treatment reduced GABA to the lowest levels of any of the experimental conditions. PA was specific for the CNS and did not affect peripheral areas. Amino oxyacetic acid, which inhibits GABA-transaminase, caused elevated GABA levels in the brain and apparently increased tumor rates in rats treated with 3-MC. Although only 3-MC and PA were tested, results suggest a relationship between CNS effects and peripheral carcinogenesis. (13 Refs) (In GER)

36. PYRAN COPOLYMER AND 7,12-DIMETHYLBENZANTHRACENE-INDUCED CARCINOGENESIS IN THE HAMSTER CHEEK POUCH.

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Arch Oral Biol; 26(10):761-767 1981

The anticarcinogenic action of pyran copolymer (PC) on 7,12-dimethylbenzanthracene (DMBA)-induced carcinogenesis in the cheek pouch of male Golden Syrian hamsters was examined. All hamsters treated topically with DMBA exhibited buccal pouch tumors after 11 wk. None of the animals receiving no treatment (Group 1) or mineral oil alone (Groups 2 and 4) developed tumors. Group 3 (saline- and DMBA-treated) and Group 5 (PC- and DMBA-treated) hamsters displayed mean tumor latent periods of 7.900 and 8.074 wk, respectively. Groups 3 and 5 exhibited mean tumor diameters of 2.7 and 3.0 mm, respectively, at 11 wk. Groups 1-4 included 6 hamsters each; Group 5 was composed of 24 hamsters. One hamster each in groups 1, 2, 3, and 5 died prior to the end of the 11-wk period. No significant difference in carcinoma incidence was observed between Groups 3 and 5 after 11.5 wk. Of Group 3 and 5 hamsters, 100% and 96%, respectively, developed carcinomas. No consistent difference in histologic appearance of carcinomas was observed between Groups 3 and 5. Mean hemagglutinin titers were higher in groups receiving PC than in the saline-treated control groups, but the difference was not significant. Analysis of immunologic findings for Groups 3 and 5 demonstrated a statistically significant difference in respective mean titers ($p = 0.01$). Organ and blood-cell changes were noted only in PC-treated animals. The results indicated that PC had little if any effect on DMBA-mediated buccal pouch carcinogenesis. (27 Refs)

37. INHIBITORY ACTION OF ASPARAGUS RACEMOSUS ON DMBA-INDUCED MAMMARY CARCINOGENESIS IN RATS.

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Int J Cancer; 28(5):607-610 1981

The present paper reports the inhibitory effect of Asparagus racemosus on DMBA-induced mammary tumorigenesis in rats of Holtzman strain. When virgin female rats, normal or primed with 17-beta-estradiol treatment, are put on diets containing 0.25%, 0.5%, 1% or 2% Asparagus root extract powder prior to their exposure to DMBA, mammary tumor incidence shows a sharp decline. (Author abstract) (39 Refs)

38. EFFECTS OF CADMIUM IN VITRO ON BENZO(A)PYRENE METABOLISM BY RAT TESTICULAR AND HEPATIC MICROSOMES (MEETING ABSTRACT).

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Toxicologist; 1(1):121 1981

Cadmium is known to have toxic effects on the testes as well as to inhibit microsomal mixed function oxidase activity in a variety of tissues. Studies were carried out to compare the actions of cadmium in vitro on testicular and hepatic metabolism of benzo(a)pyrene (BP), a compound which requires metabolic activation for its mutagenic and carcinogenic effects. Testicular and hepatic microsomes were o btained from normal male rats and incubated with BP in the presence of saturating concentrations of NADPH and varying (2 x 10(-4) M -5 x 10(-6) M) concentrations of cadmium. In liver microsomes, cadmium produced a dose-dependent decrease in the production of fluorescent metabolites (phenols). By contrast, in testicular microsomes, the lower concentrations of cadmium (2.5 and 5 x 10(-5) M) enhanced the formation of phenols whereas higher levels (greater than 1 x 10(-4) M) decreased the production of fluorescent metabolites. To determine if the changes in testicular production of phenolic metabolites might be related to alterations in competing metabolic pathways, the effects of cadmium on the activity of epoxide hydrase, an enzyme required for the production of dihydrodiol metabolites, were investigated. Cadmium produced a dose-dependent inhibition of epoxide hydrase activity in both testicular and hepatic microsomes. The effects in testes were greater than those in liver. Preliminary analysis of BP metabolites by high performance liquid chromatography further indicates that cadmium affects the production of both phenols and dihydrodiols by testicular and hepatic microsomes. The results demonstrate that cadmium alters the routes of metabolism of BP in the testes and may therefore, influence its toxicity. (no Refs)

39. ENHANCEMENT OF BENZO(A)PYRENE INDUCED SISTER CHROMATID EXCHANGES AS A CONSEQUENCE OF GLUTATHIONE DEPLETION IN VIVO.

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Toxicol Lett; 9(4):339-343 1981

The effect of decreased hepatic glutathione (GSH) concentration on sister chromatid exchange (SCE) in vivo in the bone marrow of Chinese hamsters induced by 3,4-benzo(a)pyrene (BaP) was examined. SCE were studied in differentially stained bone marrow after sc implantation of 50 mg bromodeoxyuridine, ip injection of phorone (125 or 250 mg/kg body wt) or olive oil, and injection of BaP (50 or 100 mg/kg body wt). Induction of SCE by BaP after pretreatment with 125 mg/kg phorone increased to an av 5.9 (50 mg/kg BaP) and 7.0 (100 mg/kg BaP) SCE/cell. Pretreatment with 250 mg/kg phorone resulted in SCE values of 6.8 (50 mg/kg BaP) and 7.6 (100 mg/kg BaP). Hepatic GSH content and GSH S-transferase activities were also studied after injection of phorone (125 or 250 mg/kg body wt) or olive oil. Pretreatment with 125 mg/kg phorone led to a decrease in the GSH content to 1.2 micromole/g liver but had no significant effect on GSH S-transferase activities. Pretreatment with 250 mg/kg phorone gave no further effect. Apparently the amount of GSH available is one factor responsible for the degree of detoxication of BaP. The higher SCE frequency in the absence of GSH is probably a consequence of an increased amount of reactive, mutagenic BaP metabolites. (18 Refs)

40. LEUKEMOGENIC EFFECT OF URETHANE ADMINISTERED TOGETHER WITH ESTROGENS TO MICE.

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Egeszsegtudomany; 25(3):251-255 1981

Effects of carcinogenic and noncarcinogenic substances administered together with estrogens or urethane were studied in 6-8-wk-old male CFLP mice. Each substance was administered in three individual doses during an 18-day period, and the results were evaluated after 300 days. Lung tumors and lymphomas were found in the animals treated with ethyl formate (500 mg/kg), phenylurethane (100 mg/kg), pyrene (5 mg/kg), and their combinations with diethylstilbestrol (DES: 25 mg/kg), but there was no significant difference in the percentage of tumor-bearing animals between the treated animals and the untreated controls. Other groups were treated with dimethylnitrosamine (10 mg/kg), benzo(a)pyrene (5 mg/kg), or 3-methylcholanthrene (5 mg/kg), or their combinations with DES. There was no significant difference in tumor frequency between the groups treated with the carcinogens only and those treated with the carcinogens and DES. Solid tumors in the abdominal cavity and hepatic tumor were also found in addition to lung tumors and lymphomas in the DES-treated groups. Other groups were treated with urethane with or without BCG or Escherichia coli endotoxin (ET): the carcinogenic effect of urethane was not modified by BCG and ET. In other experiments, urethane induced multiple lung tumors with and without DES, but the number of lymphomas was significantly higher in the group treated with urethane and DES than in the groups treated with urethane or DES alone. (24 Refs) (In HUN)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

41. TUMORIGENICITY OF BAY-REGION DIOL-EPOXIDES AND OTHER BENZO-RING DERIVATIVES OF DIBENZO(A,H)PYRENE AND DIBENZO(A,I)PYRENE ON MOUSE SKIN AND IN NEWBORN MICE.

Chang RL, Levin W, Wood AW, Lehr RE, Kumar S, Yagi H, Jerina DM, Conney AH
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Cancer Res; 42(1):25-29 1982

Dibenzo(a,h)pyrene [DB(a,h)P], dibenzo(a,i)pyrene [DB(a,i)P], and seven of their benzo-ring derivatives were tested for tumorigenic activity on mouse skin and in newborn mice. In the tumor studies on mouse skin, a single topical application of 50, 200, or 600 nmol of compound was followed 7 days later by twice-weekly applications of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate for 16 or 24 wk. With the exception of 2,10-difluorodibenzo(a,i)pyrene, all of the compounds had significant tumor-initiating activity at all doses tested. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene, the metabolic precursors of b ay-region diol-epoxides, had tumor-initiating activity that was equivalent to their parent hydrocarbons. Saturation of the double bond in the benzo-ring of these dihydrodiols resulted in the formation of tetrahydrodiols whose tumor-initiating activity was not significantly different from that observed with the corresponding dihydrodiols at the 50-nmol dose. The bay-region diol-epoxides of DB(a,h)P and DB(a,i)P, in which the benzylic hydroxyl group and the oxirane oxygen are trans (Isomer 2), induced significantly fewer tumors per mouse than did their dihydrodiol and parent hydrocarbon precursors. In the tumorigenicity study in newborn mice, a total dose of 87.5 nmol of the hydrocarbon divided into three ip injections was administered on the 1st, 8th, and 15th day of life, and tumorigenic activity was determined when the mice were 49 to 54 wk old. trans-1,2-Dihydroxy-1,2-dihydrodibenzo(a,h)pyrene and trans-3,4-dihydroxy-3,4-dihydrodibenzo(a,i)pyrene induced three- to eight-fold more pulmonary tumors per mouse and four- to five-fold more hepatic tumors per male mouse than the respective parent hydrocarbons. The corresponding tetrahydrodiols had no more than one-eighth of the pulmonary tumorigenic activity of the corresponding dihydrodiol. The bay-region diol-epoxide (Isomer 2) of DB(a,h)P had tumorigenic activity equal to the parent hydrocarbon but significantly less than its dihydrodiol precursor. The bay-region diol-epoxide (Isomer2) of DB(a,i)P was highly toxic, and only 19% of the mice survived to termination of the study. This diol-epoxide had significantly less tumorigenic activity towards the lung than did either its dihydrodiol precursor or the parent hydrocarbon. Notably, 20% of the surviving mice treated with the diol-epoxide of DB(a,i)P had leukemia at the termination of the study. 2,10-Difluorodibenzo(a,i)pyrene had no tumorigenic activity in newborn mice at the single dose tested. These results are discussed in relationship to the bay-region theory of polycyclic aromatic hydrocarbon carcinogenicity. (Author abstract) (27 Refs)

42. EFFECTS OF FLUORINE SUBSTITUTION ON THE TUMOR INITIATING ACTIVITY AND METABOLISM OF 5-HYDROXYMETHYLCHRYSENE, A TUMORIGENIC METABOLITE OF 5-METHYLCHRYSENE.

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Carcinogenesis; 2(10):1027-1032 1981

Tumor-initiating activity of 5-methylchrysene (5-MeC) on mouse skin was compared with that of a major 5-MeC metabolite, 5-hydroxymethylchrysene (5-HOMeC). After an initiating dose of 30 ug, with promotion by tetradecanoylphorbol acetate, 5-HOMeC induced skin tumors in 90%, with 9.5 tumors/mouse. 5-MeC resulted in 75% incidence of skin tumors with 6.2 tumors/mouse. The tumorigenic activities after a 10 ug initiating dose were: 5-HOMeC, 45% incidence and 2.6 tumors/mouse; 5-MeC, 55% incidence and 5.6 tumors/mouse. The compound 6-hydroxymethylchrysene was inactive. The tumor initiating activities of two monofluoro derivatives also were investigated to elucidate the mechanism of 5-HOMeC activation. 7-Fluoro-5-hydroxymethylchrysene (7-F-5-HOMeC) was as tumorigenic as 5-HOMeC, whereas 3-fluoro-5-hydroxymethylchrysene (3-F-5-HOMeC) was significantly less tumorigenic. The inhibition of tumorigenicity by substitution of fluorine at the 3-position, but not the 7-position of 5-HOMeC is analogous to previously described results with 5-MeC and suggests a similar mechanism of activation for both compounds. Metabolites formed upon incubation of 5-HOMeC with cofactors and the 9,000x gravity supernatant from Aroclor pretreated rats were separated by high pressure liquid chromatography. The 1,2-dihydrodiol and 7,8-dihydrodiol of 5-HOMeC were identified. The major phenolic metabolite was 1-hydroxy-5-hydroxymethylchrysene. In the in vitro metabolism of 7-F-5-HOMeC under the same conditions, 1,2-dihydrodiol was identified but not 7,8-dihydrodiol. In the metabolism of 3-F-5-HOMeC, oxidation in the 1-4 ring was inhibited relative to that observed in the metabolism of 5-HOMeC. These results suggest that 5-HOMeC is activated primarily through formation of its 1,2-dihydrodiol. (27 Refs)

43. INCIDENCE AND TYPE OF TUMORS INDUCED IN C57BL BG/BG MICE AND +/BG LITTERMATES BY ORAL ADMINISTRATION OF DMBA.

Argov S, Cochran AJ, Karre K, Klein GO, Klein G
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Int J Cancer; 28(6):739-746 1981

As an attempt to study the effect of the beige (bg) mutation on chemical carcinogenesis, 64 C57Bl/bg/bg mice and 83 +/bg littermate controls received DMBA in five weekly intragastric doses. The incidence of tumors of different histological types was monitored through observation periods ranging between 165 and 500 days. By 165 days after the first DMBA feeding, 18% of the +/bg and 31% of the bg/bg mice had developed tumors. The beige mice had a higher incidence of epithelial and non-epithelial tumors arising in cutaneous or sc sites than the controls. The total incidence of lymphomas was similar in the two groups. However, lymphomas appeared somewhat earlier in beige than in control mice. Altogether 33 +/bg and 27 bg/bg mice were followed for 500 days. By this time, 73% of the +/bg and 78% of the bg/bg mice had developed tumors. The beige group showed a higher incidence of non-thymic lymphomas than the controls. In contrast, the incidence of thymic lymphoma, cutaneous epithelial tumors and bile-duct adenomas was similar in the two groups or higher in

+/bg than in bg/bg mice. The results suggest that the bg mutation causes a certain defect in a mechanism that may prevent or delay the onset of nonthymic lymphomas and of epithelial and non-epit helial cutaneous tumors in DMBA-treated mice. The differences between the two groups were smaller than those previously reported in relation to the increased susceptibility of beige mice to certain transplanted tumors, attributed to the known defect in natural killer (NK) activity in the beige mice. The reduced differential in the DMBA system may be due to the partial reduction of NK activity, induced by the carcinogen, as reported previously and confirmed in the present study. (Author abstract) (33 Refs)

44. INITIATION/PROMOTION ASSAY FOR CHEMICAL CARCINOGENS IN RAT LIVER (MEETING ABSTRACT).

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Health Effects Research Laboratory, US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicologist; 1(1):155 1981

We have developed a short-term initiation/promotion assay in rat liver for the detection of chemical carcinogens. Male rats (175-200 gm) were po administered the chemical under test. One wk later tumor promotion by 500 ppm sodium phenobarbital in the drinking water was commenced. After 8 wk of promotion the rats were sacrificed and the liver stained and scored for gamma glutamyl transpeptidase (GGTase) positive foci. The appearance of GGTase positive foci was taken as an indication of the initiation of carcinogenesis by the chemical. In some cases partial hepatectomy was performed 24 hr prior to the administration of the test chemical in an attempt to increase the sensitivity of the assay. Acetylaminofluorene (AAF), aflatoxin B1 (AFB1) benzo(a)pyrene (BaP), diethylnitrosamine (DENA), 7,12-dimethylbenzo(a)anthracene (DMBA), dimethylnitrosamine (DMNA), N-methyl-N'-nitro-N-nitrosoguaninidine and urethane were positive in the assay while benzene (30 mmole/kg) was apparently negative. Phenobarbital promoted the response of AAF, AFB, DENA, DMBA and DMNA. Partial hepatectomy 24 hr prior to initiation increased the response of AAF, BaP, DENA and DMBA. The initiation/promotion assay in rat liver that includes 1) partial hepatectomy at 24 hr prior to administering the test chemical, 2) phenobarbital promotion and 3) GGTase foci as indication of carcinogenic activity; would appear to be sensitive to a wide variety of chemical carcinogens. (no Refs)

45. LUNG CANCER MODEL SYSTEM USING 3-METHYLCHOLANTHRENE IN INBRED STRAINS OF MICE.

Henry CJ, Billups LH, Avery MD, Rude TH, Dansie DR, Lopez A, Sass B, Whitmire CE, Kouri RE
Dept. Experimental Oncology, Microbiological Associates, Bethesda, MD, 20816
Cancer Res; 41(12):5027-5032 1981

A model system has been established for studying lung carcinogenesis using intratracheal instillation of 3-methylcholanthrene in C3H/AnfCum and C57BL/Cum x C3H/AnfCum F1 (hereafter called BC3F1/Cum) mice. The animals in these studies were screened for adventitious agents and were free thr oughout their lifetime of two important lung viruses, Sendai virus and pneumonia virus of mice. Under these conditions, the occurrence of spontaneous and chemically induced lung cancers was determined over the lifetime of the animals. Data were analyzed by the actuarial method for lung tumor probability. Probability was found to be dose and time dependent. Over 95% of the 3-methylcholanthrene-treated BC3F1/Cum and over 88% of the C3H/AnfCum mice were found at death to have pulmonary carcinomas. Tumors observed in animals which died up to 40 wk on test were almost always squamous cell carcinomas (approx 85%), while tumors which were observed in animals which died after 50 wk were mainly alveolar adenocarcinoma (approx 80%). Both tumor types metastasized widely. Spontaneous lung cancers (only alveolar adenocarcinomas were observed) occurred in these two strains at low frequency and were expressed late in life. Thus, the system described affords a suitable model to study the induction, expression, and progression of lung tumors under conditions where a vast majority of animals develop neoplasia. (Author abstract) (20 Refs)

46. EXPERIMENTAL STUDIES OF CARCINOGENESIS OF THE UTERINE CERVIX IN MICE.

Wentz WB, Reagan JW, Fu YS, Heggie AD, Anthony DD
Dept. Reproductive Biology, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Gynecol Oncol; 12(2,part2):S90-S97 1981

The histogenesis of cervical carcinomas induced in mice by coal-tar hydrocarbons or inactivated herpes simplex virus, Types 1 and 2, has been described. The lesions antedating the development of squamous cell carcinoma were similar to lesions encountered in patients with the same keratinizing type of carcinoma of the ectocervix. A theory for the development of the three grades of human cervical squamous cell carcinoma has been presented based on experimental and clinical data which demonstrate that each of the three grades of cancer consists of cells which resemble those of the tissue of origin and of the antecedent noninvasive lesion. (Author abstract) (20 Refs)

47. INDUCTION OF SKIN PAPILLOMAS IN THE SENCAR MOUSE AS A TIER 2 CARCINOGENESIS BIOASSAY (MEETING ABSTRACT).

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Health Effects Research Laboratory, Cincinnati, OH, 45268
Toxicologist; 1(1):129 1981

The Toxic Substances Control Act mandates the testing of industrial chemicals for which insufficient evidence of safety exists. One of the more critical areas in chemical carcinogenesis testing is a dependable approach to confirmatory tests (tier 2) of identifed positives at a screening level (tier 1). The present work was undertaken as part of a systematic evaluation of a series of short-term in vitro and in vivo tests which possess properties thought desirable for tier 2 testing. Experiments were design ed to determine whether the mouse skin responds to initiating doses of carcinogens selected from the major carcinogen classes administered by four routes, oral, ip, sc and topical. Experiments to date include testing of diethylnitrosamine, urethane, benzene, benzo(a)pyrene, dimethylbenzanthracene (DMBA), aflatoxin B1, methylmethane sulfonate, azobenzene, FANFT and lead acetate. Two wk following application of the initiating doses of each carcinogen a 20 wk promotion schedule involving the application of 1 ug of 12-O-tetradecanoyl phorbol-13-acetate (TPA) was initiated. On the basis of preliminary data it is apparent that papilloma development in response to chemical carcinogens varies with route of exposure. For example, it is apparent that the response to urethane administered po exceeds that observed by the topical route by 3-fold. Conversely, the response of the mouse skin to benzo(a)pyrene is more than 10-fold by the topical vs systemic routes of exposure. Route specific responses to DMBA, benzene, diethylnitrosamine and aflatoxin B1 are also apparent.

These results suggest that consideration be given to employing more than one route of exposure in testing of chemicals using the mouse skin initiation/promotion system. (no Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

48. A EUROPEAN COLLABORATIVE STUDY OF THE AMES ASSAY: I. RESULTS AND GENERAL INTERPRETATION.

Grafe A, Mattern IE, Green M
Boehringer Mannheim GmbH, Sandhofer Strasse 116, D-6800 Mannheim 31, W. Germany
Mutat Res; 85(6):391-410 1981

The Ames assay was performed for three test compounds (benzo(a)pyrene, N-nitrosomorpholine, and 2-aminoanthracene) in a collaborative study in 19 laboratories. Marked variations between test results occurred between and within laboratories; variability resulted partially from different interpretations of the guidelines, which allowed some flexibility. Results were also affected by other factors. Some variation was due to the level and quality of S9 preparations; different batches of S9 prepared in the same laboratory by a standard procedure may vary significantly in their properties. Other factors involve the number of cells used, differences in culture conditions, type and amount of solvent, number of plates used per concentration, and method of counting colonies. When results from all experiments were considered together, 60-80% were found within the half- to two-fold range of the overall median. Such a range might be considered satisfactory for a study not using rigidly standardized test conditions. Several recommendations for design and performance of future collaborative studies are given. (13 Refs)

49. EVALUATION OF TRANSFORMATION ASSAYS USING C3H 10T1/2 CELLS FOR USE IN SCREENING (MEETING ABSTRACT).

Schechtman LM, Lubet RA, Kouri RE, Sivak A, Tu AS
Microbiological Associates, Bethesda, MD, 20816
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The C3H 10T 1/2 C1 8 (10 T 1/2) cell transformation system is being evaluated independently and simultaneously in two laboratories for its utility, reliability and reproducibility as a predictive in vitro screening test for potential chemical carcinogens. Eleven known chemicals were tested using a standard protocol in the absence of exogenous metabolic activation. The polycyclic hydrocarbon carcinogens 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene (BaP) and dibenz(a,h)anthracene induced Type II and Type III foci, while the non-carcinogens phenanthrene and anthracene were non-transforming. The direct-acting agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethyl methanesulfonate and N-acetoxy-2-fluorenylacetamide (AFAA) induced little or no transformation. The procarcinogenic aromatic amines N-2-fluorenylacetamide and 2-anthramine were not active. Thus the 'standard' assay shows a range of sensitivity, depending upon the specific class of chemicals employed. To overcome such limitations, the assay has been modified by (a) cell synchronization, (b) increasing cells at risk, (c) replating treated cells ('level II transformation'), and (d) supplying exogenous metabolizing activity (eg hepatocytes, S-9). Transformation of 10T 1/2 cells was induced by MNNG and AFAA using modified protocols without a metabolic supplement. Use of an -Aroclor-1254-induced rat hepatic S-9 resulted in activation of a variety of chemicals to cytotoxic metabolites. S-9-mediated enhancement of phenotypic transformation has been thus far achieved with BaP. Additional studies employing hepatocytes for metabolic activation are in progress. Validation studies of cell populations derived from Type III foci showed that while most transformed populations grew in soft agarose, their tumorigenic potential was dependent on the strain, age and immunosuppression of host animals used. Efforts are ongoing to assess the efficacy of these different approaches in rendering the 10T 1/2 cell system responsive to diverse classes of procarcinogens and direct-acting carcinogens. Validation of the transformation system is being carried out by testing coded samples. (no Refs)

50. NEOPLASTIC TRANSFORMATION ASSAY WITH BALB/C 3T3 CELLS. ANALYSIS OF RESULTS WITH 70 CODED SAMPLES (MEETING ABSTRACT).

Sivak A, Lobb AM, Tu AS
Arthur D. Little, Inc., Cambridge, MA, 02140
Toxicologist; 1(1):131 1981

Exposure of certain populations of mouse BALB/c 3T3 cells to chemical carcinogens results in morphological transformation in the cell culture that can be identified and quantified. In the assay validation, 15 uncoded and 70 coded chemicals comprising a series of known carcinogens and noncarcinogens were tested using a standard protocol. Among the chemical classes tested, polycyclic aromatic hydrocarbons, direct-acting alkylating agents, activated aromatic amine metabolites and certain metal carcinogens gave positive responses. Aromatic amines, nitrosamines and other chemicals, such as natulan and cyclophosphamide, that require metabolic activation to exhibit activity, did not induce neoplastic transformation, although aniline was positive. The hormones ethynylestradiol, progesterone and diethylstilbesterol, which are likely epigenetic carcinogens, were not active in this system. Statistical analyses of the data reveal that: (1) the range of spontaneous transformation frequency has a mean value of 0.28 foci/plate; (2) the induced transformation frequency of the positive control (3-methylcholanthrene, 2 ug/ml) has a mean value of 2.6 foci/plate; (3) at control values above the cumulative mean, a doubling of transformation frequency in treated cultures is a statistically significant positive effect (alpha less than or equal to 0.05). At the control values below the cumulative mean, statistical significance is achieved only at higher treated to control response ratios, which rise sharply as control values approach zero. (4) The relationship of the untreated control response to the positive response is not a simple background incidence. (no Refs)

51. PROGRESSION INTO 'DEEP' RESTING STATES REQUIRED FOR CARCINOGENIC TRANSFORMATION IN CULTURES OF C3H/10T1/2 CELLS (MEETING ABSTRACT).

Miska D, Bosmann HB
University of Rochester, Rochester, NY
Toxicologist; 1(1):154 1981

We have previously shown that confluent cultures of C3H/101/2 cells progress into deeper G0 states with culture age as indicated by lengthened prereplicative lag times after serum step-up. This progression is here shown to be influenced both

by the serum concentration and the medium renewal frequency. Conditions that block this progression also inhibit carcinogenic transformation. Cells were seeded at 100/1.6 mm well in Eagle's Basal Medium containing 10% heat-inactivated fetal calf serum, and treatment wells received 1.0 or 5.0 ug 3-methylcholanthrene in 0.5% acetone from 24-48 hr. At confluency the wells were divided into 4 groups by serum concentration and renewal frequency: 10%-4d, 10%-1d, 3%-4d, 3%-1d. Cell counts of representative untreated wells were made daily from seeding until day 27. The 3%-4d, 3%-1d, and 10%-4d, groups achieved steady-state densities of 1.1, 2.0, and 2.3 x 10(5) cells/well, respectively, but the 10%-1d group continued to grow and had a density of 7.0 x 10(5) cells at 27 days. Transformation, as measured by type III foci 42 days after seeding, was completely inhibited in this group. Transformation in th e other groups was independent of density but was influenced by the carcinogen's concentration. At 42 days the GO depth for each group was measured by nuclear labeling with [3H]-thymidine after serum step-up. The groups that showed transformation had progressed into GO beyond what is seen in freshly confluent cells, whereas the untransformed 10%-1d group had not, indicating that the cultures must progress into deep resting states for carcinogenic expression. (no Refs)

52. DIFFERENTIAL INDUCIBILITY OF CHROMOSOME ABERRATIONS AND SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS IN VARIOUS MAMMALIAN CELL LINES.

Ikeuchi T, Sasaki M
(c/o Sasaki) Chromosome Res. Unit, Hokkaido Univ., Sapporo 060, Japan
Mutat Res; 90(2):149-161 1981

A variety of mammalian cell cultures were examined for inducibility of chromosomal aberrations (CA) and sister chromatid exchanges (SCE) by the indirect mutagens cyclophosphamide (CP), dimethylnitrosamine (DMN), and benzo(a)pyrene (BP). Sixteen cell lines were examined for response to CP. All rat ascites hepatoma cell lines showed a significant increase in frequencies of both SCE and CA in a dose-dependent manner. Several rat esophageal tumor cell lines showed an extremely high sensitivity to CP, with significant yields of SCE and CA obtained at much lower concentrations compared to other cell lines. Seven cell lines were examined for their responsiveness to DMN. AH66-B, R1 and R3 cells, which showed a significant response to CP, were also sensitive to DMN in induction of CA. SCE frequency increased only slightly, however. Of the four cell lines studied for BP sensitivity, GHE cells showed the highest response to BP; frequencies of both SCE and CA were increased up to 3.8-and 6.9x. AH66-B and B-13 were moderately sensitive. HE2144 was almost insensitive but showed slightly increased frequency of SCE. (28 Refs)

53. INDUCTION OF GENE MUTATIONS BY BENZ(A)PYRENE DURING METABOLIC ACTIVATION.

Pashin IuV, Bakhitova LM
Inst. General Genetics, Moscow, USSR
Biull Eksp Biol Med; 91(9):327-329 1981

The mutagenic activity of benz(a)pyrene (BP) was studied in Chinese hamster diploid cell line V-79. Incubation of the cell culture in media containing BP (5-25 ug/ml) and microsomal activating mixture resulted in a dose-dependent increase in the yield of gene mutations. (13 Refs) (In RUS)

54. SEX-LINKED LETHAL FREQUENCIES PRODUCED BY 7,12-DIMETHYLBENZ(A)ANTHRACENE IN FIVE DROSOPHILA MELANOGASTER WILD STRAINS.

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Dept. of Biological Sciences, Univ. Idaho, Moscow, ID, 83843
Mutat Res; 90(3):255-260 1981

Drosophila melanogaster strains fed 1.0 or 4.0 milliM 7,12-dimethylbenz(a)anthracene (DMBA) mixed into larval food displayed varying sex-linked lethal frequencies. Differences appeared to be related to levels of activating enzymes that metabolize DMBA. (17 Refs)

55. MICRONUCLEI IN PERIPHERAL BLOOD ERYTHROCYTES: A CONVENIENT INDICATOR OF IN VIVO CYTOGENETIC DAMAGE (MEETING ABSTRACT).

MacGregor JT, Wehr CM, Langlois RG, Gould DH
U.S. Department of Agriculture, Western Regional Research Center, Berkeley, CA
Toxicologist; 1(1):40 1981

Treatment of Swiss mice with nitrogen mustard (NM) 7,12-dimethylbenz(a)anthracene (DMBA) or cyclophosphamide (CP) results in a peak incidence of micronucleated polychromatic RBC (PCEs) in blood which is approx of equal magnitude to the peak incidence in bone marrow PCEs. The peak incidence in peripheral blood was in each case observed on the day following the peak incidence in bone marrow and was 35/1000 PCE, 91/1000 PCE, and 14/1000 PCE for NM (2.5 mg/kg, ip), DMBA (40 mg/kg, ip), and CP (25 mg/kg, ip), respectively. The 65 control animals from these experiments av 1.6/1000 PCE. Approx equal incidences of micronucleated PCEs were observed in blood from the orbital sinus, heart, ventral tail vessels, and severed axillary vessles. Use of peripheral blood rather than bone marrow for general genetic screening provides at least equal sensitivity, permits multiple sampling (less than 10 ul of blood provides an ample number of cells) and simplifies sample preparation. The uniformity of the cell population in peripheral blood may make automated scoring feasible. We have developed a simple fluorescent staining procedure using pyronin Y (for RNA) and Hoechst 33258 (for DNA) which permits identification of micronuclei and differentiation of immature from mature RBC. The staining method is applicable to either methanol-fixed smears on slides or formalin-fixed blood cells in suspension, and may serve as the basis of a flow cytometric procedure for rapidly scoring, micronucleated cells. (no Refs)

56. APPLICATION TO BENZO(A)PYRENE FED RATS OF A PROPOSED SHORT-TERM IN VIVO CARCINOGEN SCREENING PROTOCOL (MEETING ABSTRACT).

Boyd JN, Missibeck N, Campbell TC, Babish JG, Stoewsand GS
Department of Preventive Medicine, Cornell University, Ithaca, NY
Toxicologist; 1(1):36 1981

This study was undertaken to determine if induction of presumptive pre-cancerous lesions by benzo(a)pyrene (BP) could be predicted in a short-term treatment by demonstration of urinary mutagenesis and by increased concentration in the blood of the oncodevelopmental protein alpha fetoprotein (AFP). Existence of pre-cancerous lesions was confirmed by gamma glutamyl transpeptidase staining of liver sections from treated animals. Male weanling F344 Schf rats were fed semi-purified diets containing 0, 1, 100 or 1000 ppm BP with or without 0.05% sodium phenobarbital for six to thirteen wk. Blood was obtained at one to two wk intervals by cardiac puncture and

plasma AFP levels were determined by sandwich type radio immunoassay. Urine was collected for eight hr during the sixth wk of treatment. Glucuronidase-treated specimens were tested for mutagenesis in salmonella typhimurium strains TA98 and TA100 with and without microsomal activation. Liver specimens were stained for gamma glutamyl transpeptidase (GGT) activity and examined for presence of foci of altered cells. Those treatments resulting in elevated plasma AFP and mutagenic urine were associated with development of GGT-positive hepatic cell foci. This protocol could be applied early in the range finding phase of a carcinogenesis bio-assay to aid in selection of substances for long-term testing. (no Refs)

57. QUANTITATIVE MUTAGENESIS AND MUTAGEN SCREENING WITH MAMMALIAN CELLS: TOWARD A COMPREHENSIVE CHINESE HAMSTER GENETIC TOXICITY SYSTEM (MEETING ABSTRACT).

Hsie AW
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Toxicologist; 1(1):40 1981

We have employed Chinese hamster ovary (CHO) cells to develop and define a mutational assay at the hypoxanthine-guanine phosophoribosyl transferase (HGPRT) locus. Coupled with S9 metabolic activation system, the CHO/HGPRT assay permits quantification of gene mutation and cytotoxicity induced by various classes of mutagens including 3 aklanesulfonates, 2 alkylsulfates, 3 nitrosoguanidines, 3 nitrosoureas, 19 heterocyclic mustards (ICR compounds), 6 platinum(II)chloroammines, 7 quinolines, 8 nitrosamines, 3 haloethanes, 4 polyaromatic hydrocarbons. Such study elucidates the structure-activity relationship for a given class of direct-acting mutagens. All carcinogens investigated, except ICR 191, showed mutagenic activity; and all noncarcinogens were non-mutagenic. The CHO/HGPRT system can also simultaneously measure mutagen-induced chromosome aberration and sister chromatid exchange (SCE) which led to the development of the Multiplex CHO Genetic Toxicity Assay. Recent studies have shown that it is feasible to determine chromosomal deletion and loss using a CHO/human hybrid cell line and to develop a Chinese hamster system for studies of induction of mutation at the HGPRT locus, chromosome aberration and SCE of peripheral blood lymphocytes. The use of such a comprehensive Chinese Hamster Genetic Toxicity System consisting of these four assays at the cellular and organismic level should enable a sensitive and reliable identification of suspected environmental mutagens. (no Refs)

58. STUDIES ON THE MUTAGENIC EFFECTS OF EXTRACTS DERIVED FROM AIRBORNE PARTICULATES WITHIN ONE YEAR IN DIFFERENTLY BURDENED AREAS USING THE AMES TEST.

Dehnen W, Tomingas R, Pitz R
Med. Institut fur Umwelthygiene, Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):351-366 1981

Season variations of the mutagenicity of extracts of suspended matter in air sam ples collected at monthly intervals in 1978 from three sites were assayed by the Ames test. The three sites were Duisburg (DU; mines), Dusseldorf (D; a residential city), and Krahm (K; rural district). Mutagenicity was tested in the presence of both S-9 and NADPH and with each cofactor alone. Results are presented as the number of revertants related to air vol, wt of suspended matter, wt of dried extract and to the amount of benzo(a)pyrene (BP) in the extract. Mutagenicity varied according to the BP concentration in the atmosphere with values highest in winter, lowest in summer. When mutagenicity was based on BP content, it was nearly constant throughout the yr at site DU or rose in summer (sites D and K). These results indicate that the larger part of the pollutants may originate from the same sources as BP (eg incomplete combustion). Direct mutagenicity (assayed without activating system) was somewhat higher in winter than in summer. However, these differences are minimal or lacking when mutagenicity was expressed as number of revertants per wt suspended matter or dried extract. Mutagenicity reached a max in summer, provided the number of revertants was related to BP concentration. The latter results indicate that the direct acting mutagens present in the air originated from other sources than that of BP (eg, automobile exhaust). Mean values of mutagenicity related to number of revertants per dry wt and wt of suspended matter did not differ among the three sites. It can be assumed that composition of particulate matter may be similar with respect to mutagens regardless of the level of pollution. (10 Refs) (In GER)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

59. CALCULATION OF REACTIVITY INDICES FOR BENZ(A)ANTHRACENE AND BENZO(A)PYRENE AND THEIR APPROXIMATIVE MODELS OF COMPLEX WITH ENZYME EPOXIDASE.

Miertus S, Majek P
Inst. Polymers, Slovak Acad. Sciences, 809 34 Bratislava, Czechoslovakia
Neoplasma; 28(4):441-446 1981

By theoretical methods of quantum mechanics an interaction between carcinogenic hydrocarbons - benz(a)anthracene, benz(a)pyrene - and various groups simulating an effect of enzyme oxidase has been studied. If accord is to be achieved with formation of epoxides of these compounds in vivo according to the bay region theory (ie, in A region) an interaction between the enzyme involving an electron-acceptor group and the bay region of hydrocarbon under simultaneous steric hindrance of the K region is necessary. Another possibility of obtaining the highest reactivity in the A region is to assume the formation of the radical cation as a first intermediate in the interaction with enzyme. (Author abstract) (9 Refs)

60. STRUCTURAL ASPECTS OF CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).

Glusker JP
Institute for Cancer Research, 7701 Burholme Avenue, Philadelphia, PA, 19111
Molecular Structure and Biological Activity: A Symposium on Biologically Active Molecules, (Twelfth Congress), August 26-28, 1981, Buffalo, New York. International Union of Crystallography 89 pp., 1981.

The process of carcinogenesis by polycyclic aromatic hydrocarbons (PAH) involves the enzymatic 'activation' of the hydrocarbon to a diol epoxide and, it is presently believed, alkylation of DNA by this alkylating agent. The shape and size of the PAH is important. If it is too large or too small it is not as potent a carcinogen. The optimal size approaches that of a steroid or a base pair. This shape may also have significance in the interaction of the PAH with the hydroxylating enzyme. In

addition, methyl substitution for hydrogen in the 'bay area' of a PAH, which characteristically causes distortions as a result of steric effects, often enhances carcinogenic activity. Studies in several systems have led to the conclusion that flatness is not a criterion for carcinogenicity and that total intercalation of the hydrocarbon cannot occur. The benzoflavone that inhibits the 'activation' process has been shown by x-ray studies to be nonplanar. Interactions between hydroxyl and epoxide groups in the same molecule may affect reactivity. The immediate aim of these studies is to determine what effects alkylation by an activated PAH can have on DNA. The structure of a nucleoside alkylated by chloromethyl PAH has been studied and it is shown, as predicted, that the base and PAH portion lie almost perpendicular to each other. Some possible effects of such alkylation on DNA structure will be discussed. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

61. CHEMICAL CARCINOGENESIS.

Farber E
Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
N Engl J Med; 305(23):1379-1389 1981

Fundamental concepts related to the causation, prevention, and therapy of cancer in humans are reviewed, with emphasis on mechanistic aspects. Topics include cancer as a chronic multistage process, initiators and initiation (initiators, activation and metabolism of procarcinogens, possible molecular targets for ultimate carcinogens, DNA repair, carcinogen metabolism in human tissues, initiation), promoters and promotion (promoters, promotion, subsequent steps - progression and transfection, diet and carcinogenesis, chemotherapy and carcinogenesis), and new bioassays for carcinogens and promoters. Illustrations of (1) the current view on activation of benzo(a)pyrene to benzo(a)pyrene 7,8 dihydrodiol,9,10 epoxide, (2) sites of interactions of activated forms of carcinogens with the four DNA bases, and (3) steps in the initiation of carcinogenesis with chemicals are presented. Later phases of chemical carcinogenesis, ie post-initiation phenomena including promotion, and the relative quantitative importance of exogenous or endogenous c hemical carcinogens in patients with cancer not related to smoking are not sufficiently understood. (118 Refs)

62. ADVANCES IN THE METABOLIC ACTIVATION OF CARCINOGENS.

Ivanetich KM
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, Cape Province, South Africa
S Afr Cancer Bull; 25(1/2):105-116 1981

Of the known chemical carcinogens, an ever-increasing number require metabolic activation to elicit their mutagenic and carcinogenic effects. In a review, it is noted that the enzymes known as cytochrome P-450 alone or in conjunction with other enzymes are involved in this activation. The activated metabolites may initiate carcinogenesis by covalently binding to selected sites on nuclear DNA in somatic cells. Detailed pathways are presented for a number of carcinogens, such as chlorinated ethylenes, aflatoxin B1, acetylaminofluorene and benzpyrene. (22 Refs)

63. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.

Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

A review is presented of incidence, risk factors, and chemical and environmental agents involved in induction or promotion of cancer of the gastrointestinal system. Presence of ingested agents in foods and experimental and clinical evidence for cancer causation are discussed. Carcinogenesis is considered with respect to the esophagus (nitrosamines, mycotoxins, promotional factors), stomach (nitrites and polycyclic hydrocarbons, mycotoxins, agricultural products, polychlorinated biphenyls, experimental carcinogens), and large bowel (nitrites, aflatoxins, diet, carrageenan, chemical carcinogens: nitroso compounds, biphenyls, symmetrical 1,2-dialkylhydrazines and azoalkanes and azoxyalkanes). Chemicals with known gastric tumor induction capability in animals are tabulated from published reports. (74 Refs)

64. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R
Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

A review is presented of the effects of air pollution on defense mechanisms of the body which may in turn account for differences in individual reactivity to such pollution. Some important findings relating to this problem follow: deterioration of lung clearance after inhalation of NO2 and lead chloride; damage to alveolar macrophages by air-borne particulates in vitro and in vivo; enhanced activation of C3 complement fraction under the influence of air pollutants; higher frequency of enlarged tonsils and lymph nodes, of pathogenic bacteria on tonsillar surfaces, and of relatively lower lysozyme concentrations in children living in urban or industrialized areas; decreased resistance to infections related to inhalation of O3 or a lead aerosol; immuno-suppressive effect of heavy metals and organic compounds; allergic reactions to many chemicals; detoxification and toxification, eg formation of ultimate carcinogens, and of organic molecules; induction or inhibition of benzo(a)pyrene metabolism by particulate extracts or by CO, NO2, and lead; deficiency of DNA-repair in disease conditions predisposing to development of cancer; tendency, in allergic subjects, to a relatively lower incidence of cancer; adaptation to the effect of CO and SO2. These facts, and others not cited, support a close connection between various defense mechanism, air pollution, and its effects on the human organism. (55 Refs) (In GER)

65. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.

Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

The role of prostaglandins (PG) in tumor initiation, promotion, and metastasis is reviewed. Results from tests in Salmonella typhimurium and mice suggest that prostaglandin endoperoxide synthetase (PES) may play a role in activating carcinogenic compounds, such as malondialdehyde, although findings may have been affected by carcinogenic impurities. Arachidonic acid may trigger cooxidation of noncarcinogens, such as benzo[a]pyrene to carcinogenic forms. The kidney may play

a role in toxicity or carcinogenicity because of its physiological composition and high blood flow. PES appears to trigger carcinogens when introduced into dog kidneys in vivo. PG may play a role in tumor promotion by tetradecanoyl phorbol acetate (TPA). TPA treatments result in increased PG levels. Nontumorigenic phorbol esters do not increase PG levels. Some inhibitors of PES and lipoxygenases have been found to inhibit tumor growth in mice. PG apparently play a role in proliferation and differentiation of cells and therefore may affect tumor growth. PG appear to inhibit proliferation of monocyte and T lymphocyte precursors and to enhance proliferation of erythrocytes. Manipulation of PG levels may offer a means of controlling tumor growth and metastasis. (161 Refs)

66. THE MILD CIGARETTE - IS THERE ANY?.

Carlens E
Toraxkliniken, Karolinska sjukhuset, Stockholm, Sweden
Lakartidningen; 78(39):3370-3373 1981

Lung cancer, which had been the rarest form of tumor 50 yr ago, is now the most frequent tumor, affecting almost exclusively smokers. However, the vast majority of the smokers do not develop lung cancer, which indicates the involvement of predisposition. Benzo(a)pyrene, present in the tar, is noncarcinogenic, but its metabolite formed under the action of arylhydrocarbon hydroxylase, which occurs at varying levels in humans, is. It is almost impossible to induce lung cancer by tar and benzo(a)pyrene in experimental animals. Only an insignificant increase in lung cancer incidence was observed among 6,000 asphalt workers who have been inhaling benzo(a)pyrene at concentrations several times higher than those to which smokers are exposed for 20 yr. There has been recently a certain slowdown in the increase in lung cancer incidence, but it has been much smaller than the reduction in the tar content in cigarettes. This smaller than expected decrease may be due to increased cigarette consumption due to lower nicotine content and to deeper inhalation of the smoke. (5 Refs) (In SWE)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

DIETARY FACTORS IN CARCINOGENESIS

1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLU TANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xinchua Zazhi; 1(1):1-4 1981

In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

In GER

7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Molin GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaar seweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

Mutat Res; 87(2):81-142 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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PHILIP C. HANAWALT Stanford University	*Cellular Responses to Damaged DNA*	#VK03 54 min.
CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
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LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

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CHEMICAL CARCINOGENESIS

Polycyclic Aromatic Hydrocarbons and Related Compounds

SERIES CK07 No. 82/05

MAY, 1982

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. MUTAGENICITY OF AIRBORNE PARTICLES FROM A NONINDUSTRIAL TOWN.

Whong WZ, Stewart J, McCawley M, Major P, Merchant JA, Ong TM
Div. Respiratory Diseases, Natl. Inst. Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV, 26505
Environ Mutagen; 3(6):617-626 1981

The mutagenicity of air particles from a nonindustrial university town was exami ned. Air samples were collected during June-December, 1980. Dichloromethane extracts of all samples exhibited mutagenic activity in Salmonella typhimurium TA98, but secondary ethyl acetate/methanol extracts did not. No mutagenic activity was observed in extracts of blank filters. The number of revertants ranged from 34-355/mg particles and from 35-455/10 cubic meters of air. Mutagenic activity of samples collected in June and July did not require S-9 activation, while the mutagenicity of samples collected in October, November, and December was enhanced by S-9 activation. Dichloromethane extracts were also mutagenic using the arabinose-resistant assay system; such mutagenicity was dose-dependent and could be detected at a sensitivity of 1 cubic meter air/plate. Mutagenic activity in TA98 was found in acidic and polynuclear aromatic fractions but not in neutral or basic fractions. Samples of coal fly ash from a university power plant extracted with dichloromethane were mutagenic. (21 Refs)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

2. IDENTIFYING HUMAN CELLS CAPABLE OF METABOLIZING VARIOUS CLASSES OF CARCINOGENS.

Aust AE, Antczak MR, Maher VM, McCormick JJ
Dept. Microbiology, Michigan State Univ., East Lansing, MI, 48824
J Supramol Struct; 16(3):269-279 1981

Metabolism of tritiated benzo(a)pyrene (BP) to aqueous-acetone soluble forms and inhibition of cellular DNA synthesis were used to identify human cells capable of metabolizing various classes of carcinogens. Hydrocarbon-metabolizing activity assay (HMAA) and DNA synthesis inhibition assay were optimized and the results on 15 human epithelial cell lines were compared. Four classes of carcinogens were examined: polycyclic hydrocarbons (PH), aromatic amines (AA), heterocyclic hydrocarbons, and nitrosamines. Each of the classes was activated by one or more cell lines. Cells with very low metabolizing activity, such as NF, showed little or no cytotoxic response when exposed to BP at concentrations up to 30 uM for 48 hr. Biological results (cytotoxicity, mutagenicity, and DNA binding) suggest that the HMAA is a useful prescreen for identifying human cells that metabolize BP to biologically active forms. Cells that appeared capable of metabolizing PH or AA according to the methods were found to produce metabolites which were cytotoxic to cocultivated human xeroderma pigmentosum fibroblasts after 48 hr exposure to the carcinogen. (28 Refs)

3. CONJUGATION PATHWAYS IN HUMAN BRONCHIAL CARCINOMA CELL LINES.

Gibby EM, Mehta R, Ellison M, Cohen GM
Toxicology Unit, Dept. Pharmacology, Sch. Pharmacy, Univ. London, 29 Brunswick Square, London WC1N 1AX, England
Biochem Pharmacol; 30(24):3333-3336 1981

Human bronchial carcinoma cell lines in monolayer cell culture were used to study the conjugation of 1-naphthol and 3-hydroxybenzo(a)pyrene, two phenolic substrates. Cell lines, able to metabolize 1-naphthol to glucuronic acid and sulfate ester conjugates, showed a predominance of glucuronidation. This is in sharp contrast to normal human peripheral lung which metabolizes these phenolic substrates predominantly to the sulfate ester conjugates. The bronchial tumor cell lines do not all have the same conjugation pattern and they differ in the metabolism of phenolic substrates when compared to normal peripheral lung. The cell lines generally show that sulfate ester conjugation was either reduced or absent. In some cases, dependent on the type of tumor the cell line was derived from, glucuronic acid conjugation was elevated. Initial sub-cellular studies with a poorly differentiated epidermoid cell line (Ben) demonstrated that this line had an active UDP-glucuronosyltransferase (Km 33 uM and Vmax 1.8 nmoles min-1.mg protein(-1)), using 1-naphthol as substrate. However, this cell line was unable to form significant amounts of sulfate ester conjugates, due to either low sulfotransferase activity, or an inability to generate adenosine 3'-phosphate 5'-sulfatophosphate (PAPS). (Author abstract) (20 Refs)

4. INTERTISSUE VARIATION IN BENZO(A)PYRENE METABOLISM BY HUMAN SKIN, LUNG AND LIVER IN VITRO.

Milo GE, Trewyn RW, Tejwani R, Oldham JW, Douglas WH
Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH
Aerosp Med Biol; (224):173 1981

An environmental agent benzo(a)pyrene (B(a)P), is shown to transform human skin fibroblasts in vitro. This fossil fuel combustion product and other polynuclear hydrocarbons have exhibited a requirement to be biotransformed to their ultimate carcinogenic forms to induce transformation. B(a)P diol-epoxides are the most cited candidates as ultimate carcinogens. Results suggest that either the ultimate form of the carcinogen is different for fibroblasts and epithelial cells or the quantitative generation of hydroxylated metabolites is not required for neoplastic transformation in fibroblast cells. If hydroxylation is required, then the site of hydroxylation may be the significant factor. Present evidence suggests that in B(a)P treated fibroblasts the activation of B(a)P in the cell takes place other than the microsomal P450 complex, presumably in the nucleus. (Author abstract) (no Refs)

5. CYTOTOXIC EFFECTS AND METABOLISM OF BENZO[A]PYRENE AND 7,12-DIMETHYLBENZ[A]ANTHRACENE IN DUODENAL AND ILEAL EPITHELIAL CELL CULTURES.

Quaroni A, Isselbacher KJ
Gastrointestinal Unit, Massachusetts General Hosp., Boston, MA, 02114
JNCI; 67(6):1353-1362 1981

Two epithelial cell lines have been established from the duodenum (IEC-17) and the ileum (IEC-18) of outbred germ-free Crl:CD(SD)GN rats. They have a very similar morphology and ultrastruct ure, a normal rat diploid karyotype, comparable

growth rates, and a similar set of surface antigens as detected with monoclonal antibodies specific for intestinal epithelial cell surface proteins in vivo. Both cell lines do not grow in soft agar and when injected into syngeneic animals do not form tumors. The toxic effects of benzo[a]pyrene (BP) and 7,12-dimethylbenz[a]anthracene (DMBA) were studied in these two cell lines. The IEC-18 cells were found to be much more sensitive to both chemicals than the IEC-17 cells. In particular, at concentrations greater than 1 ug/ml, DMBA completely and irreversibly inhibited cell proliferation in the IEC-18 cells, whereas it produced a less marked and reversible inhibition in the IEC-17 cells. The metabolism of BP and DMBA to water-soluble products was studied; BP was apparently metabolized at similar rates in the two cell lines, whereas a striking difference was observed with DMBA, which was metabolized at a rate 10-15x greater in the IEC-18 cells than that in the IEC-17 cells. These results suggest that cultured cell lines derived from different portions of the intestinal tract have similar properties in vitro, but they may have very different responses to chemical carcinogens. (Author abstract) (34 Refs)

6. STUDIES ON THE IN VITRO TRANSFER OF DNA BINDING BENZO[A]PYRENE METABOLITES FROM RAT HEPATOCYTES TO HUMAN FIBROBLASTS.

Nordenskjold M, Svensson SA, Jernstrom B, Moldeus P, Dock L, Soderhall S
Dept. Clinical Genetics, Karolinska Hosp., S-104 01 Stockholm, Sweden
Carcinogenesis; 2(11):1151-1160 1981

The release and reabsorption of benzo[a]pyrene (BP) metabolites were studied in isolated rat hepatocytes incubated with BP. There was a rapid uptake of BP by the hepatocytes which was followed by an excretion of organic as well as water-soluble metabolites. Upon further incubation the BP-dihydrodiols and BP-phenols were reabsorbed by the cells and finally excreted as water-soluble conjugates. The metabolism of BP by the hepatocytes also resulted in the formation and release of reactive intermediates to the incubation medium. The DNA-binding intermediates released from the cells were consistent with trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene-9,10 oxide(s) and 9-hydroxybenzo[a]pyrene-4,5-oxide(s). The BP-metabolites were found to bind to hepatocyte and fibroblast DNA. The degree of DNA binding was estimated as the formation of DNA strand breaks. BP metabolites formed within the hepatocytes and transferred to the fibroblasts were found to induce DNA strand breaks in the latter cells. Addition of DNA to the medium markedly decreased the fraction of single stranded DNA in these cells. Under conditions where the excretion from hepatocytes of BP-phenols and BP-dihydrodiols were increased, the amount of DNA strand breaks in the fibroblasts increased. (Author abstract) (72 Refs)

7. COMPARATIVE METABOLISM OF 7,12-DIMETHYLBENZ(A)ANTHRACENE AND SEVERAL FLUORINATED ANALOGUES IN SYRIAN HAMSTER EMBRYO CELL CULTURE AND IN SPRAGUE-DAWLEY AND LONG-EVANS RATS IN VIVO.

Oravec CT
Ohio State University, Columbus, OH
Diss Abstr Int [B]; 42(5):1844-B 1981

The metabolites resulting from the rat liver microsomal oxidation of 7-12,dimethylbenz(a)anthracene (DMBA) and its fluoro analogs were compared to the metabolites from treatment of Syrian hamster embryo (SHE) cell cultures with [3H]DMBA, [3H]2F-DMBA, [14C]5F-DMBA and [3H]11F-DMBA, SHE cells in culture were exposed to each of the above DMBA analogs up to 24 hr and the metabolites both within and outside the cell (in the media) were isolated and analyzed by high pressure liquid chromatography and fluorescence spectroscopy. Metabolites were also separated into their free and conjugated components by alumina chromatography and treated with either B-glucuronidase or sulfatase enzymes to identify their conjugated components. These studies were subsequently compared to the in vivo analysis of DMBA and 2F-DMBA in Sprague-Dawley and Long-Evans fifty day old, female rats. These two strains were chosen because of their sensitivity and resistance, respectively, to assult by DMBA and the subsequent development of mammary tumors. The DMBA and 2F-DMBA metabolites isolated from the urine of these rats were analyzed using similar techniques as those described above for the SHE cell metabolism. Several differences between the two species were noted. (no Refs)

8. PRESENCE OF BENZO[A]PYRENE METABOLIZING ACTIVITIES IN ISOLATED RAT LIVER NUCLEOLI.

Lafarge-Frayssinet C, Alexandrov K, Rimbaut C, Dansette PM, Mousset S, Frayssinet C
Institut de Recherches Scientifiques sur le Cancer, BP No. 8, 94802 Villejuif Cedex, France
Carcinogenesis; 2(11):1189-1193 1981

A benzo[a]pyrene (B[a]P) hydroxylase activity and epoxide hydrolase (EH) activity have been found in rat liver nucleoli obtained from untreated (C) and 3-methylcholanthrene (3-MC) pretreated rats. A comparison of the enzyme activities was made in rat nuclei and nucleoli. Light and electron microscopic observations of nucleolar preparations did not reveal significant contamination either by intact nuclei or by nuclear membranes, and glucose 6-phosphatase, a marker of microsomal activity, was not detected in our nucleolar preparations. NADPH cytochrome c-reductase could be measured in C and 3-MC nuclei and very low but detectable activity was found in the nucleoli. Nucleolar preparations revealed significant hydroxylating activity, which was inducible by 3-MC in nuclei but not in nucleoli. The presence of EH in nucleoli was demonstrated with phenanthrene 9,10-oxide and B[a]P 4,5-oxide, but the nucleolar activities were lower than those obtained using intact nuclei. The addition of 1,1,1-trichloropropene 2,3-oxide completely inhibited EH activity. Furthermore the presence of covalently-bound metabolites of B[a]P formed in isolated nucleoli was demonstrated by cytofluoromicroscopy. (Author abstract) (30 Refs)

9. DEVELOPMENTAL ONSET OF MIXED-FUNCTION OXIDASE ACTIVITY IN PREIMPLANTATION MOUSE EMBRYOS.

Filler R, Lew KJ
Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN, 37830
Proc Natl Acad Sci USA; 78(11,part2):6991-6995 1981

Two-cell embryos, obtained from the C57BL/6N and DBA/2N strains, were cultured in media that supported in vitro differentiation and that contained [3H]benzo[a]pyrene. High-pressure liquid chromatography of the activated intermediates formed during in vitro early embryonic development indicated that the onset of polynuclear aromatic hydrocarbon activation coincided with blastocyst formation. Comparison of individual oxygenated intermediates metabolically formed from embryos genetically 'responsive' or 'nonresponsive' to aromatic hydrocarbons revealed significant quantitative differences in the production of dihydrodiol, quinone, and phenolic derivatives. In

addition to exhibiting basal mixed-function oxidase activity, blastocysts were also responsive to enzymatic induction when exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. The presence of operative metabolite-detoxifying pathways was also assayed. Enzymatic treatment of water-soluble metabolites with beta-glucuronidase or arylsulfatase revealed that neither glucuronic acid conjugates nor sulfate ester derivatives were present. These data, therefore, provide direct evidence that late preimplantation mouse embryos (day 3 1/2 of gestation) are similar to later developmental stages in having the enzymatic capability for xenobiotic activation and enzyme induction but are dissimilar with respect to their detoxification mechanism(s). Moreover, the ability of preimplantation embryos to activate directly polynuclear aromatic hydrocarbon to bioreactive intermediates may be of importance in assessing the ontological susceptibility of the developing embryo to carcinogenic or teratogenic chemicals. (Author abstract) (27 Refs)

10. ARYL HYDROCARBON MONO-OXYGENASE INDUCTION IN HAMSTER EMBRYONIC CELLS EXPOSED TO FOSSIL SYNFUEL PRODUCTS (MEETING ABSTRACT).

Schuresko DD, Griffin GD

Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Carcinogenic and mutagenic polynuclear aromatic (PNA) compounds are abundant in the products and wastes of many fossil fuel conversion processes, and pose a major long-term hazard to the health of plant personnel and to the environment. Methods for estimating the extent of human exposure to PNAs and for screening personnel hypersusceptible to PNA toxicity are clearly required components of the developing synthetic fossil fuel industry's health protection practice. To this end, we are studying the dose-dependent induction of the aryl hydrocarbon mono-oxygenase (AHM) enzyme system in cultured cells exposed to coal-derived tars and oils. Fibroblasts from the 15-day-old fetuses of Syrian hamsters are isolated by successive subculturing, grown in media containing coal-derived liquids, then harvested and assayed for AHM activity, as measured by the rate of benzo[a]pyrene (BP) metabolism. The 'direct' assay, in which the rate of decrease of BP fluorescence in suspensions of intact fibroblasts is measured, is the proven assay of choice as regards assay reliability, although we have also used the standard assay as described by Nebert and Gelboin for comparison. High-performance liquid chromatographic analysis (according to the procedure of Selkirk and Macleod) of the extractable metabolites of 3H-labelled BP was used to identify specific metabolites and to confirm the direct fluorometric AHM activity determinations. We have observed that the hamster AHM enzyme is typically 8-fold inducible by a 1.4-ppm concentration of benzo[a]anthracene in the growth medium, and is 4-fold inducible by a 50 ppb concentration of a gasifier tar in the medium. Adaptation of this AHM assay to flow cytofluorometry for measurement of AMH activity in human lymphoblastoid cells and in lymphocytes subpopulations is in progress. (3 Refs)

BINDING TO CELLULAR MACROMOLECULES

11. COVALENT BINDING OF BENZO(A)PYRENE TO DNA IN FISH LIVER.

Varanasi U, Stein JE, Hom T

NMFS Environmental Conservation Div., Northwest and Alaska Fisheries Center, 2725 Montlake Blvd. East, Seattle, Washington, 98112

Biochem Biophys Res Commun; 103(2):780-787 1981

The extent of covalent binding of benzo(a)pyrene (BaP) intermediates to hepatic DNA and protein was determined in English sole exposed po to 3H-BaP. Radioactivity in the liver represented 0.6% of the administered dose at 16 hr. The liver concentration of BaP-derived radioactivity did not change significantly from 16-336 hr after BaP administration; greater than 98% of the total radioactivity in liver was in the form of the organic solvent- and water-soluble metabolites. Detectable binding of BaP intermediates to liver DNA was observed between 6 and 336 hr after BaP exposure. No statistically significant change was observed in the binding values for DNA during the 2 wk exposure; the extent of BaP binding to liver protein did not change significantly over the 2 wk period. The av of all specific activity values for protein (58 +-51) was not significantly different from the av value for DNA (44 +-39). The results indicated that the extent of BaP binding to fish liver DNA is comparable to values reported for mammalian tissues susceptible to polycyclic aromatic hydrocarbon-induced neoplasms; chemical modification of hepatic DNA was observed for at least 2 wk after a single exposure to BaP. (30 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

12. AGE-DEPENDENT CHANGES IN PREVALENCE, SIZE AND PROLIFERATION OF ARTERIAL LESIONS IN COCKERELS; II. CARCINOGEN- ASSOCIATED LESIONS.

Penn AL, Batastini GG, Albert RE

Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016

Artery; 9(5):382-393 1981

Age-dependent changes in the prevalence, frequency, size, and proliferation of aortic lesions in cockerels injected weekly with the 7,12-dimethylbenz(a)anthracene (DMBA) were determined. Cockerels 4 wk old received im injections of DMBA (10 mg/kg body wt) every wk dissolved in dimethylsulfoxide (DMSO). Control groups recieved only DMSO. Animals were sacrificed at 4 wk intervals between 8-20 wk of age. Microscopic lesions were observed in the abdominal aortas of all animals regardless of age or treatment. These findings confirmed previous observations, that carcinogens do not primarily induce formation of new lesions. Injections of DMBA resulted in an accelerated increase in lesion size compared to that seen in untreated animals. Such sharp increases in lesion size were not seen in untreated animals The time and rate of appearance of large lesions were accelerated. A burst of lesion cell proliferation in cockerels after 12 wk of DMBA treatment was noticed. No equivalent changes were noticed in the control groups. Results indicated, that within the lesion mass there

may be a subpopulation of cells that can proliferate more readily than the majority of lesion cells in response to chronic exposure to DMBA and other carcinogenic agents. (8 Refs)

13. HISTOLOGICAL EVIDENCE OF 'ESTROGENIC PROPERTIES' OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Valero D, Drouhault R, Vanhems E, Bousquet J, Blanquet P
Unite 53, I.N.S.E.R.M., Domaine de Carreire, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France
Cell Mol Biol; 27(2/3):263-269 1981

DMBA (7,12-dimethylbenz(a)anthracene) and estradiol provoke in rat pituitaries an increase of prolactin cells number and of hormone synthesis. It is a transitory effect. Both enhance equally G6PD activity, this enzyme acting for an end product of a functional estradiol receptor. This increased reactivity persists during mammary tumor growth. These data added to previously published results, support the hypothesis that carcinogen would act in part by 'estrogen-mimetic' properties. (Author abstract) (25 Refs) (In FRE)

14. MOLECULAR BIOLOGY OF ENVIRONMENTAL AROMATIC HYDROCARBONS. PROGRESS REPORT, 1 JAN. -31 DEC. 1980.

Weiss SB
Chicago Univ., Chicago, IL
Sci Tech Aerosp Rep; 19(2):240 1981

Three different aspects of hydrocarbon action are investigated: the biochemical effect of benzo(a)pyrene-diol-epoxide on the replication of Simian virus 40; the reaction of benzo(a)pyrene-7,8-diol with viral DNA; and the effect of PAH derivatives on RNA transcription. (Author abstract) (no Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

15. INHIBITION OF METHYLCHOLANTHRENE-INDUCED SKIN CARCINOGENESIS IN HAIRLESS MICE BY DIMETHYL SULFOXIDE.

Iversen OH, Thorud E, Volden G
Inst. Pathology, Univ. Oslo, Oslo 1, Norway
Carcinogenesis; 2(11):1129-1133 1981

Hairless mice were given five topical applications of 470 nmol 20-methylcholanthrene (MCA) at 1 wk intervals. In one experimental group the MCA was dissolved in reagent grade acetone alone, in another group it was dissolved in a mixture consisting of 50% acetone and 50% dimethyl sulfoxide (DMSO). A control group received the mixed solvent alone. The animals were observed for development of papillomas and malignant tumors during 75 wk. The group treated with MCA in acetone/DMSO had a higher mortality than the two other groups. The admixture of 50% DMSO to the solvent had a significant inhibitory effect on tumor and cancer rates and on cancer yield, whereas no effect could be observed on the tumor yield. Hence, 50% DMSO in the solvent has a moderate, but significant, inhibitory effect on MCA-induced skin carcinogenesis. Similar inhibitory effect of DMSO on the promotion phase in two stage-carcinogenesis protocols have been reported in the literature. The biochemical mechanisms behind this effect are unknown. (Author abstract) (15 Refs)

16. COMPARISON OF THE EFFECT OF BUTYLATED HYDROXYTOLUENE ON N-NITROSOMETHYLUREA AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS.

King MM, McCay PB, Kosanke SD
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Cancer Lett; 14(3):219-226 1981

The effects of butylated hydroxytoluene (BHT) on nitrosomethylurea (NMU)- and 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary tumors were examined. Female Sprague-Dawley rats were fed either control diets or diets plus 0.3% BHT, and further divided into NMU-treated, DMBA-treated, or nontreated groups. DMBA was administered at 10 mg in 1 ml stripped corn oil intragastrically at 50 days of age. NMU was administered at 5 mg/100 g body wt iv in the tail vein at 50 days of age. A 100% incidence of tumors was seen in rats treated with DMBA and on the control diet. The incidence was reduced to 54% by addition of BHT to the diet. No difference in tumor incidence was seen in NMU-treated animals with or without addition of BHT. The differences in tumor prophylaxis may reflect the fact that DMBA is metabolized by the monooxygenase system but NMU is not. (30 Refs)

17. PHENOLS AND OTHER COMPONENTS OF OIL SHALE TARS AND ASBESTOS AS FACTORS MODIFYING THE CARCINOGENIC ACTION OF BENZO(A)PYRENE.

Bogovski P, Kung A, Winkmann F
Inst. Experimental and Clinical Medicine Hiiu Str. 42, 200016 Tallin, USSR
Arch Geschwulstforsch; 52(1):49-55 1982

The modifying action of phenols and other components (paraffins, olefins, naphthenes, aromatic hydrocarbons, neutral oxygen compounds) present in oil shale tar on the carcinogenic effects of benzo(a)pyrene (BP) and chrysotile asbestos dust was studied. Epicutaneous tests were performed on 500 C57Bl mice divided to 10 different treatment groups. The skin tumors found in this series included benign papillomas and malignant squamous epithelial carcinomas and basalomas. The tar fractions containing phenols and neutral oxygen compounds moderately potentiated the tumor-inducing action of BP, while the tar components alone induced at best papillomas. Another experimental series with 500 2.5-3-mo-old rats treated with BP, tar fractions and asbestos dust intratracheally revealed that the lung tumor incidence was highest after simultaneous administration of BP, asbestos dust and tar phenols. Asbestos dust potentiated the carcinogenic action of BP to the same extent as the tar phenols, whereas the latter had no such effect on the potency of asbestos dust. The lung tumors included epidermoid carcinomas, bronchial and alveolar adenocarcinomas and reticulosarcomas. (9 Refs) (In GER)

18. SERUM CHOLESTEROL AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY CARCINOGENESIS.

Klurfeld DM, Kritchevsky D
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Cancer Lett; 14(3):273-278 1981

Tumor formation induced by po administration of 5 mg of the mammary carcinogen dimethylbenz(a)anthracene in female Sprague-Dawley rats was studied as a function of serum cho-

lesterol level. Changes in serum cholesterol were induced by subjecting animals to one of three diets: (a) semipurified cholesterol-free (SP), (2) the same diet with 1.5% cholesterol and 0.5% bile salts added (CB), and (3) diet CB until treatment with DMBA, followed by diet SP thereafter. No significant differences were discernible in body wt due to diet or carcinogen administration throughout the study. Tumor incidence was similar in all groups (69-73%). Total tumor yield was significantly greater in Group 2 than in the other groups. Tumor vol and wt were similar in the three groups. Latency period of tumor appearance was 2 wk longer in Group 1 than in other groups. Group 2 had at least 2x as many palpable tumors as Group 1, while Group 3 was intermediate in occurrence. (20 Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

19. DIAPLACENTAL INITIATION OF NMRI MICE WITH 7,12-DIMETHYL-BENZ[A]ANTHRACENE DURING GESTATION DAYS 6-20 AND POSTNATAL TREATMENT OF THE F1-GENERATION WITH THE PHORBOL ESTER 12-O-TETRADECANOYLPHORBOL-13-ACETATE: TUMOR INCIDENCE IN ORGANS OTHER THAN THE SKIN.

Goerttler K, Loehrke H, Hesse B, Milz A, Schweizer J
Inst. Experimental Pathology, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W. Germany
Carcinogenesis; 2(11):1087-1094 1981

The tumor spectrum and tumor incidence in organs other than the skin were investigated in the 12-O-tetradecanoylphorbol-13-acetate (TPA) treated F1-generation of 13 groups of NMRI mice which had been initiated by a single intragastric dose of 7,12-dimethylbenz[a]anthracene during Days 6,8, and 10-20 of pregnancy. Promotion by topical application of TPA to the back skin was carried out twice per wk 12 wk after birth over a period of 26 wk. The forestomach epithelium represented the only organ in which statistically significant 2-stage carcinogenesis could be demonstrated. A promotion effect could be seen in tumors of the Harderian gland, of the liver of male animals and on the development of both benign and malignant tumors of the lung in both sexes. Promotion treatment therefore led to an activation of initiated tumor cells in those organs in which a very sensitive, more or less narrowly spaced oncogenic determination period exists. (Author abstract) (12 Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

20. A MICROSUSPENSION ADAPTATION OF THE BACILLUS SUBTILIS 'REC' ASSAY.

McCarroll NE, Keech BH, Piper CE
Dept. Toxicology, Hazleton Lab. America, Inc., 9200 Leesburg Turnpike, Vienna, VA, 22180
Environ Mutagen; 3(6):607-616 1981

Sixty-six high mw or poorly soluble compounds were tested for mutagenicity in the Bacillus subtilis 'rec' assay. Six of 13 mutagenic aromatic amines were detected as preferential inhibitors of B subtilis M45. Nine polycyclic aromatic hydrocarbons, including benzo(a)pyrene, 3-aminopyrene, 7,12-dimethylbenz(a)anthracene, and 3-methylcholanthrene, which do not elicit a genotoxic effect in Escherichia coli, were found to have preferential inhibitory activity towards M45. Anthracene, phenanthrene, and pyrene were inert. Dimethylnitrosamine and diethylnitrosamine both diminished growth of M45, as did a variety of other nitrosamines and hydrazines. The noncarcinogenic antimetabolite 5-fluoro-2'-deoxyuridine was genotoxic to M45. Acetamide, ethyl carbamate, methyl carbamate, and thiourea were inactive against M45, confirming results obtained using E Coli MSA and other microbial systems. All mutagenic alkylating agents except Captan were genotoxic in M45. In contrast to results obtained in E coli, 4-nitrobiphenyl was active in the M45 system. The lack of response in E coli may result from cell wall impenetrability of the compound. The contribution of solvents to toxicity in the B subtilis and E coli MSA systems is discussed. (13 Refs)

21. THE INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY K-REGION EPOXIDES AND SOME DIHYDRODIOLS DERIVED FROM BENZ[A]ANTHRACENE, DIBENZ[A,C]ANTHRACENE AND DIBENZ[A,H]ANTHRACENE.

Pal K
Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Mutat Res; 84(2):389-398 1981

Benz[a]anthracene (BA), dibenz[a,c]anthracene (DB[a,c]A), dibenz[a,h]anthracene (DB[a,h]A), and some of their metabolites were studied for induction of sister chromatid exchanges (SCE) in cultured Chinese hamster ovary cells. BA and 1,2; 5,6-; 8,9-; and 10,11-diols induced some SCE, but they were not as active as either benz[a]anthracene 5,6-oxide, which induced an approx 2-fold increase in SCE at 1 ug/ml, or trans-3,4-dihydro-3,4-dihydroyxbenz[a]anthracene. Despite the strong cytotoxicity of DB[a,c]A, it did not induce SCE. However, all DB[a,c]A metabolites tested (1,2-; 3,4-; and 10,11-dihydrodiols) induced SCE in a dose-dependent manner; trans-1,2-dihydro-1,2-dihydroxybenz[a,c]anthracene (4 ug/ml) induced a greater than 4-fold increase in SCE. DB[a,h]A was only weakly active. Trans-3,4-dihydro-3,4-dihydroxydibenz[a,h]anthracene was the most active DB[a,h]A metabolite, producing a greater than 3-fold increase in SCE at 2 ug/ml. Dibenz[a,h]anthracene 5,6-oxide actively induced SCE in a dose-dependent manner, whereas the 5,6-and 1,2-diols were almost inactive. K-region 5,6-epoxides derived from BA and DB[a,h]A were more active than the parent hydrocarbon in inducing SCE. Data suggest that when activated, the three polycyclic aromatic hydrocarbons studied can be metabolized to the ultimate carcinogen in CHO cells possessing some microsomal monooxygenase. (35 Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

22. ELECTROSTATIC MOLECULAR POTENTIAL CONTOUR MAPS GENERATED FROM AB INITIO MODPOT/VRDDO/MERGE WAVE FUNCTIONS OF CARCINOGENIC 3-METHYLCHOLANTHRENE AND ITS METABOLITES.

Hariharan PC, Kaufman JJ, Petrongolo C
Dept. Anesthesiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Int J Quantum Chem; 20(5):1083-1095 1981

Electrostatic molecular potential contour maps were calculated for 3-methylcholanthrene (3-MCA), its metabolites 3-MCA 7,8-oxide and 3-MCA 9,10 oxide,and the stereoisomers 3-MCA 9,10-dihydrodiol-7,8-epoxide A beta beta and 3-MCA 9,10-dihydrodiol-7,8-epoxide A alpha beta alpha. Results show that the electrostatic molecular potential contour maps may be used to indicate favored positions of attack for electrophilic species, such as 'electrophilic' oxygen to form an epoxide as well as for positive ion attack; maps for 3-MCA indicate the favored site for attack and pathways. The maps around 3-MCA 9,10-oxide and 3-MCA 9,10-dihydrodiol-7,8-epoxide indicate the directional preferences for proton ass isted epoxide ring opening. By convention, atoms below the plane of the remaining rings of 3-MCA are shown on the maps as dotted, while atoms above the plane are shown as dashed. Maps around the 3-MCA dihydrodiols indicate that for certain stereoisomers the 'electrophilic' oxygen will prefer to attack from below, but for other isomers the oxygen will attack from above. Mapping provides insight into stereochemical preference for formation of different 3-MCA 9,10-dihydrodiol-7,8-epoxides. (20 Refs)

REVIEWS AND OTHER RELATED STUDIES

23. POLYCYCLIC HYDROCARBON METABOLISM: A PLETHORA OF PHENOMENA.

Estabrook RW, Saeki Y, Chacos N, Capdevila J, Prough RA
Dept. Biochemistry, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235
Adv Enzyme Regul; 19:3-17 1981

Studies of benzo(a)pyrene metabolism by liver microsomes have revealed a complex pattern of products formed. The distribution of products generated depends on the types of cytochromes P-450 present and the mechanism of oxidation reactions catalyzed. It is proposed that cytochrome P-450 may function to catalyze the oxidation of benzo(a)pyrene not only by a NADPH-dependent monooxygenation type reaction, but also concomitantly by a peroxidatic type reaction. In particular, attention is directed to the role of the latter type of reaction for the formation of benzo(a)pyrene quinones. The pathways for the metabolic generation of quinones, as well as the reactivity of hydroquinones with oxygen, provide additional pathways for the formation of highly reactive, toxic products which may contribute to the alterations of cellular characteristics that result in either tumor growth or cell death. (Author abstract) (43 Refs)

24. REFERENCE MATERIALS.

Josephson J
No affiliation given
Environ Sci Technol; 15(12):1408-1412 1981

Definition of standard and certified reference materials (SRMs and CRMs, respectively), their uses in calibration and validation of pollutant analysis, and criteria for their preparation are discussed. SRMs, which are produced by the National Bureau of Standards (NBS), are well characterized, homogeneous, stable materials with specific properties measured by one definitive method, such as isotope dilution mass spectrometry, or two or more independent methods, such as UV spectrophotometry. Examples of SRMs include 'Urban Particulate Matter' and 'River Sediment.' No particular components are 'sought' in preparation of SRMs and no SRMs are prepared for a specific carcinogen, mutagen, or pollutant. Prices for SRMs offered by NBS typically range from 60-300 dollars per unit. CRMs, many of which are satisfactory for calibrating or validating analytical systems, procedures, or results, are produced by private laboratories inside and outside the United States. Since relatively few CRMs for suspected carcinogenic polynuclear aromatic hydrocarbons (PAH) are available, members of the European Economic Community (EEC) have launched a project to supply more calibration or reference materials. EEC project objectives include determination and collection of physicochemical spectra for suspected environmental carcinogens, initiation of mutagenicity testing, and production of high purity carcinogens as CRMs. At present 14 PAH CRMs are available from the Bureau of Reference in Belgium and 14 more are in preparation. (no Refs)

25. HEALTH AND SAFETY IMPLICATIONS OF ALTERNATIVE ENERGY TECHNOLOGIES. III FOSSIL ENERGY.

Walsh PJ, Etnier EL, Watson AP
Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Environ Manage; 5(6):483-494 1981

Potential human health and safety concerns associated with coal gasification and liquefaction, recovery of oil from shale and tar sands, and enhanced natural gas recovery are discussed. The primary health concern with coal conversion processes is the potential for exposure to carcinogens, mutagens, and teratogens such as polycyclic aromatic hydrocarbons. Studies have shown that oils with lower boiling points (less than 260 C) have little carcinogenic activity in mice. However carcinogenic activity increases as the temperature in the process streams increases. Median length of latent period preceding cancer induction in mice shows an inverse correlation to the boiling point of oil. Direct human evidence is incomplete. Preliminary research indicates that synthetic crudes are more carcinogenic than natural crudes. (54 Refs)

26. OCCUPATIONALLY RELATED CARCINOGENESIS.

Waite DE
Dept. Family Medicine, Fee Hall, Michigan State Univ., East Lansing, MI, 48824
JAOA; 80(5):350-355 1981

The epidemiology of industrial carcinogenesis is discussed. The association between cancers of the urinary bladder and occupational exposure to workers in the German coal tar industry was first made in 1895 by Rehn. Cancer of the nose associated with chromate production was reported in 1890, and lung cancer from the same exposure in 1912. During the 1940s and

1950s the marked expansion of industry led to a significant increase in the number of observed relationships between occupational exposure and subsequent development of cancer. The Occupational Safety and Health Administration (OSHA), established in 1970, determines standards for exposure to carcinogens in industrial operations. OSHA currently exercises stringent controls over 19 specific chemicals which it labels as 'cancer specific agents.' Mechanisms of chemical carcinogenesis, primary carcinogens, and secondary carcinogens are also discussed. (42 Refs)

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Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
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Jorgensen NK, Cohr KH
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Ioannides C, Delaforge M, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
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4. CARCINOGENIC, MUTAGENIC, TERATOGENIC WORKSHOP.
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5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.
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DIETARY FACTORS IN CARCINOGENESIS

6. NUTRITION AND CANCER: A REVIEW.
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
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Gynecol Oncol; 12(2,part2):S7-S24 1981

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11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
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12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
Kalmaz EV, Kalmaz GD
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Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
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MODIFICATION OF CARCINOGENESIS

15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
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Gynecol Oncol; 12(2,part2):S98-S110 1981

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Hautarzt; 32(11):601-606 1981
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. HEALTH AND ECOLOGICAL ASSESSMENT OF POLYNUCLEAR AROMATIC HYDROCARBONS.

Santodonato J, Howard P, Basu D, Lee SD, Grant L
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Syracuse, NY, 13210
J Environ Pathol Toxicol 5(1): 364 pp., 1981.

A multimedia approach is taken to the environmental hazards of polycyclic organic matter (POM). Data on physical and chemical properties, sampling and analytical methods, environmental levels, sources of contamination, environmental transport and fate, human exposure, health effects (including toxicology, epidemiology, and occupational health), and ecological effects are reviewed. The term POM has been used to describe the carcinogenic polycyclic aromatic hydrocarbons (PAH), such as benzo(a)pyrene, and their nitrogen analogs, the aza- and imino-arenes. Other related compounds believed to be environmental degradation products of PAH are also included in the category of POM. The actual components selected in a particulate sample should be based on both cost effectivness of the analytical methodology and representativeness of the carcinogenic potential. Generalizations regarding the levels of aza- and carbonyl-arenes in various media are precluded due to the limitations of available data. Atmospheric contamination by POM is the result of combustion or pyrolysis of hydrocarbon materials. Levels of POM in soil are the result of atmospheric deposition, although other sources such as coke oven water effluent have been noted. Available information suggests that bioaccumulation of PAH may be species-specific. Food is the major environmental source of POM exposure in humans. Although POM are found widely in man's environment, it is not clear whether these agents may affect the ecological balance. Data indicate that POM may accumulate in some invertebrate species. Whether transfer of POM through the food chain occurs is not known. Animal studies showing that various POM are rapidly metabolized and excreted support the contention that biomagnification is an unlikely possibility. (960 Refs)

2. THE ROLE OF OCCUPATIONAL POLLUTION IN THE ETIOLOGY AND PREVENTION OF BRONCHOPULMONARY CANCER.

Anastasatu C, Morgenstern H, Bernea D, Cristea M
Clinica de ftiziologie, I.M.F., Bucharest, Romania
Rev Ig [Ig]; 30(2):111-121 1981

Occupational risk factors of bronchopulmonary cancer were analyzed in 525 patients (423 men and 102 women) with bronchopulmonary cancer. Occupational exposure to carcinogenic and potentially carcinogenic industrial substances (asbestos, polycyclic aromatic hydrocarbons, iron, chromates, tar, asphalt, arsenic, nickel, aldrin, ethylene, benzene, copper, ammonia, polyurethane, cyclamate) was established in 310 men and 42 women. The median age of the exposed patients was 52 yr compared with 61 yr for the unexposed ones. Smokers accounted for 94.5% of the 525 patients, men for 81.5%, exposed occupationally for 73%, patients 50-69 yr old for 68%, and alcoholics for 43%. The av wt of the risk factors was 11.77 for smokers, 4.36 for men, 1.79 for occupationally exposed, and 7.2 for patients 50-69 yr old. Occupational exposure appeared to exert its effect only in conjuction with other risk factors, such as smoking, alcoholism, and urbanization. (34 Refs) (In RUM)

3. MUTAGENIC, TERATOGENIC OR TOXIC SUBSTANCES IN THE PREGNANT WOMAN WHICH MAY BE EN COUNTERED IN THE WORKING ENVIRONMENT.

Franc MC, Meunier A, Catilina P
No affiliation given
Arch Mal Prof Med Trav Secur Soc; 42(3):183-194 1981

Chemical and physical mutagenic and teratogenic agents and toxic substances to which pregnant women can be exposed in the working environment are reviewed. The occupational mutagens include benzene, benzo(a)pyrene, vinyl chloride and aflatoxins. Exposure of experimental animals to carcinogens during pregnancy caused increased tumor frequency in the first three generations. (196 Refs) (In FRE)

4. CHEMISTRY AND MUTAGENICITY OF SHALE OIL.

Guerin MR, Ho CH, Rao TK, Epler JL
Oak Ridge Natl. Lab., Oak Ridge, TN
Proceedings of the Joint US-USSR Workshop on the Health and Environmental Effects of Oil Shale Development, held in Tallinn, USSR, June 22, 1981. Available from National Technical Information Service, Springfield, VA, as DE81023196:, 12 pp., 1981.

The chemical class distribution of bacterial mutagens in a shale oil is compared to that from a petroleum crude oil and those from two coal-derived oils. Mutagenicity is found to be due to alkaline and neutral-polar polycyclic aromatic compounds in all cases. The greater mutagenicities of the petroleum substitutes is due to the presence of larger quantities of heteroatom-containing polycyclic aromatics. (Author abstract)

5. APPLICATION OF HIGH PERFORMANCE CHROMATOGRAPHIC TECHNICS TO THE QUANTITATION OF HYDROCARBONS IN MARINE BIOTA.

Friocourt MP, Berthou F, Dreano Y, Marchand M
Laboratoire de Chromatographie, Service de Biochimie, ERA CNRS no 784, Faculte de Medecine, B.P. 815, 29279 Brest Cedex, France
Analusis; 9(10):468-476 1981

Parallel determinations by UV spectrofluorimetry and high performance chromatography (liquid and gas) were performed on marine biota for the identification of hydrocarbons (HC) such as benzanthracene, benzopyrene,etc. Influence of selectivity of the liquid phase on the separation of HC was determined. The choice of internal standards permitted the easy and exact quantification of HC by high performance chromatographies. (24 Refs) (In FRE)

PHARMACOKINETICS AND METABOLISM

OF POLYCYCLIC AROMATIC HYDROCARBONS

6. ACTIVATION OF BENZO(A)PYRENE AND 2-ACETAMIDOFLUORENE TO MUTAGENS BY MICROSOMAL PREPARATIONS FROM DIFFERENT ANIMAL SPECIES: ROLE OF CYTOCHROME P-450 AND P-448.

Ioannides C, Parkinson C, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Xenobiotica; 11(10):701-708 1981

The metabolic activation of benzo(a)pyrene and 2-acetamidofluorene to mutagens was studied with liver microsomal preparations from rat, guinea-pig, hamster and mouse, untreated or pretreated with phenobarbitone or 3-methylcholanthrene. Liver microsomal preparations from all animal species a ctivated benzo(a)pyrene, that from mouse being the most efficient. Similarly, microsomal preparations from guinea-pig, hamster and mouse could activate 2-acetamidofluorene, but that from rat exhibited very weak activity. Activation of benzo(a)pyrene into mutagenic intermediates by liver microsomal preparations was increased for all animals except mouse by pretreatment with 3-methylcholanthrene. In contrast, pretreatment with phenobarbitone decreased the activation by microsomal preparations from all species. Activation of 2-acetamidofluorene by liver microsomal preparations from rat and guinea-pig, but not mouse and hamster, was increased by pretreatment of the animals with phenobarbitone. Pretreatment with 3-methylcholanthrene decreased the activation of this carcinogen by microsomal preparations from all species. The metabolic activation of benzo(a)pyrene is catalyzed by cytochrome P-448 but not cytochrome P-450. The activation of 2-acetamidofluorene to mutagens may involve, in addition to the mixed-function oxidases, other microsomal enzyme systems. (Author abstract) (29 Refs)

7. RELATIONSHIPS BETWEEN MICROSOMAL METABOLISM, DNA DAMAGE AND ADDUCT BINDING IN POLYCYCLIC HYDROCARBON-EXPOSED LUNG (MEETING ABSTRACT).

Haski R, Stewart BW
Department of Pathology, University of New South Wales, Kensington, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Preparations of isolated lung DNA from rats treated by intra-tracheal instillation of 3-methylcholanthrene (3MC) may be distinguished from control preparations by the extent of structural damage to the nucleic acid. In the study to be described, damage to DNA was determined by benzoylated-diethylaminoethyl cellulose chromatography. To analyze the relationship between metabolism of 3MC and subsequent DNA damage, the effect of modifiers of cytochrome P-450 (P-450) on both parameters was examined. Initially, measurement was made of P-450 content of rat lung at various times after administration of the hydrocarbon. In this manner experimental conditions for the use of an inducing dose of 3MC were determined and criteria were available to examine the efficacy of carbon tetrachloride-inhalation as a means of inhibiting 3MC metabolism. Animals were then treated either with an inducing dose of 3MC or by prior exposure to carbon tetrachloride to perturb microsomal metabolism of the carcinogen. The subsequent effect, on 3MC-induced DNA damage and repair, was determined. In addition, the co-valent binding of 3MC to lung DNA was assayed using LH-20 chromatography. The findings indicate that the extent of polycyclic hydrocarbon-induced DNA damage in lung may be subject to wide variation as a consequence of exposure to agents which modifiy the rate of carcinogen metabolism. (no Refs)

8. METABOLISM AND BINDING OF BENZO(A)PYRENE AND 2-ACETYLAMINOFLUORENE BY SHORT-TERM ORGAN CULTURES OF HUMAN AND RAT BLADDER.

Moore BP, Hicks RM, Knowles MA, Redgrave S
Sch. Pathology, Middlesex Hosp. Medical Sch., Riding House St., London W1P 7LD, England
Cancer Res; 42(2):642-648 1982

The ability of organ cultures of normal human and rat bladder to metabolize the polycyclic hydrocarbon, benzo(a)pyrene (BP), and the arylamine, 2-acetylaminofluorene, has been studied. Cultures were maintained for 0 to 6 days in a chemically defined medium before incubation with [3H]BP (0.3 to 0.5 uM) or 2-[14C]acetylaminofluorene (18 to 25 uM) for 24 hr. Ethyl acetate-soluble and water-soluble metabolites were produced from both compounds by both species. The ethyl acetate extracts from [3H]BP-treated human cultures contained 9,10-dihydro-9,10-dihydroxybenzo(a)pyrene, 7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, and 3-hydroxybenzo(a)pyrene. Rat bladder cultures produced similar metabolites but in slightly different proportions. Ethyl acetate-soluble products of 2-[14C]acetylaminofluorene from human cultures contained 7-hydroxy-2-acetylaminofluorine, 9-hydroxy-2-acetylaminofluorene, 2-aminofluorene, and N-hydroxy-2-acetylaminofluorene. Rat bladder cultures produced similar metabolites, but 2-aminofluorene was found in relatively higher proportion. Hydrolysis by beta-glucuronidase of the water-soluble products produced from both carcinogens gave ethyl acetate-extractable derivatives. These hydrolyzable glucuronide conjugates were relatively more abundant following metabolism of the carcinogens by the rat than by the human cultures. Covalent binding to DNA occurred with [3H]BP in both human (19.7 +-13 pmol/mg DNA) and rat cultures (22.8 +-8.6 pmol/mg DNA). As with other human tissues, considerable variation (50-fold) was observed between individuals. The results demonstrate that both human and rat bladder epithelium can metabolize known potent carcinogens and, in the case of BP, can effect covalent binding between the products of metabolism and the urothelial cell DNA. In theory, carcinogenesis in the urinary bladder could thus be initiated by carcinogens produced or excreted in the urine without the necessity for their prior metabolism elsewhere in the body. (Author abstract) (66 Refs)

9. ENZYMATIC CONTROL OF REACTIVE METABOLITES DERIVED FROM AROMATIC FOREIGN COMPOUNDS.

Oesch F
Pharmakologisches Institut der Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Chimia; 35(10):405-406 1981

The relative importance of individual enzymes in biological activation of carcinogenic metabolites of aromatic compounds was studied using Salmonella typhimurium mutants and suspensions of liver microsomes. In control and phenobarbital-induced microsomes epoxide hydroxylase (EH) efficientl y inactivated the metabolites. In 3-methylcholanthrene-induced microsomes EH had one weak multiphasic inactivating effect. (16 Refs)

BINDING TO CELLULAR MACROMOLECULES

10. FORMATION AND REMOVAL OF 7,12-DIMETHYLBENZ[A]ANTHRACENE-NUCLEIC ACID ADDUCTS IN RAT MAMMARY EPITHELIAL CELLS WITH DIFFERENT SUSCEPTIBILITY TO CARCINOGENESIS.

Tay LK, Russo J
Experimental Pathology Lab., Dept. Biology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
Carcinogenesis; 2(12):1327-1333 1981

The susceptibility of the rat mammary gland to 7,12-dimethylbenz[a]anthracene (DMBA)-induced carcinogenesis is max when DMBA is fed to young virgin rats, diminishing with increasing age and becoming almost nil when pregnancy and lactation occur prior to carcinogen administration. This present study was carried out to determine whether these differences in susceptibility to DMBA are related to the ability of the gland to form and/or remove DMBA-nucleic acid adducts. Primary mammary epithelial cell cultures derived from young virgin (YV), old virgin (OV) and parous (P) Sprague-Dawley rats were treated in vitro with [3H]-DMBA for 24 hr. Hydrolysates of DNA isolated from these cells were chromatographed on Sephadex LH-20 columns. In cells from the three groups of animals, the chromatographic profiles were qualitatively similar with three 3H-labeled products eluting in the region expected for hydrocarbon-nucleoside adducts. This similarity in profiles suggested that identical DMBA-nucleic acid adducts are generated in each group. The chromatographic data are also consistent with the hypothesis that the hydrocarbon-DNA adducts of DMBA were generated through reactions of a 'bay-region' diol-epoxide of DMBA with DNA. Excision of DMBA-DNA adducts was investigated by measuring the time-dependent decrease in specific activity of the less dense parental DNA peak following centrifugation on alkaline CsCl gradients. Within 48 hr post-DMBA treatment, P cells removed approx 36% of the adducts from DNA with YV and OV cells removed only 24% and 12% of the adducts respectively. In addition, P cells excised the adducts at a rate 1.5 and 5x faster than either YV or OV cells. These results suggest that the lower susceptibility of the parous rat towards DMBA-induced carcinogenesis may be due not to the generation of different DMBA-DNA adducts, but to a more efficient DNA repair mechanism that is the result of increased gland differentiation through the process of pregnancy and lactation. (Author abstract) (56 Refs)

11. THE METABOLIC ACTIVATION OF DIBENZ[A,C]ANTHRACENE.

Hewer A, Cooper CS, Ribeiro O, Pal K, Grover PL, Sims P
Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Carcinogenesis; 2(12):1345-1352 1981

In rat liver microsomal preparations, the 10,11-dihydrodiol of dibenz[a,c]anthra cene (DBA) is metabolized to r-10,t-11-dihydroxy-t-12,13-oxy-10,11,12,13 tetrahydrodibenz[a,c]anthracene (anti-DBA 10,11-diol 12,13-oxide), the anti isomer of a non-bay-region diol-epoxide of DBA. When 3H-labelled DBA or trans-10,11-dihydroxydibenz[a,c]anthracene were metabolized in this system in the presence of DNA or when 3H-labelled DBA was added to primary cultures of hamster embryo cells, covalent reactions of hydrocarbon metabolites with DNA occurred. The chromatographic characteristics of the radioactive hydrocarbon-deoxyribonucleoside adducts formed in these reactions were examined using Sephadex LH20 column chromatography and high pressure liquid chromatography. The results showed that whilst some of the radioactive hydrocarbon-deoxyribonucleoside adducts formed were indistinguishable from adducts that were formed when anti-DBA 10,11-diol 12,13-oxide reacted with DNA, other, unidentified adducts, which did not apparently rise from reactions of this diol-epoxide with DNA, were also present. Hydrocarbon-nucleoside adducts were not detected in hydrolysates of nucleic acids that were isolated from mouse skin that had been treated in vivo with DBA. (Author abstract) (30 Refs)

12. A COMPARISON OF THE CARCINOGEN-DNA ADDUCTS FORMED IN RAT LIVER IN VIVO AFTER ADMINISTRATION OF SINGLE OR MULTIPLE DOSES OF N-METHYL-4-AMINOAZOBENZENE.

Tillis DL, Straub KM, Kadlubar FF
(c/o Kadlubar) Div. Carcinogenesis, Food and Drug Admin., Environmental Protection Agency, Natl. Center Toxicology Res., Jefferson, AR, 72079
Chem Biol Interact; 38(1):15-27 1981

The compound N-methyl-4-aminoazobenzene (MAB) is believed to be metabolized in the liver to an electrophilic N-sulfonyloxy ester which binds covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. A single dose of MAB is not sufficient for complete carcinogenic activity, so we sought to identify the MAB-DNA adducts present in rat liver after multiple oral doses of [3H]MAB. The MAB was administered by intubation at a level of 0.2 mmol/kg for 1, 3 or 4 doses and animals were sacrificed at 8 hr after the last dose. Hepatic DNA was isolated by extraction and hydroxylapatite chromatography and was enzymatically hydrolyzed to MAB-mononucleoside adducts, which were quantitated by high pressure liquid chromatography (HPLC). After three doses, N2-dG, C8-dG, and an unknown adduct were detected. By four doses, these accounted for 51%, 25% and 23% of the total adducts. This data is consistent with rapid removal of the C8-dG derivative and the relative persistence of the N2-dG and the unknown adduct. The latter was shown to exhibit chromatographic and pH-dependent solvent partitioning properties that were identical to a product also present in DNA treated with the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene. Analysis of this adduct by field desorption mass spectrometry and, after perdeuteromethylation, by electron mass spectrometry, indicated the structure to be a deoxyadenosin-N6-yl derivative substituted through an aromatic ring of MAB. Further analysis of 270 MHz 1H-NMR spectroscopy allowed complete assignment of the MAB and adenyl resonances and was uniquely consistent with a 3-(deoxyadenosin-N6-yl)-MAB structure. Since this persistent adduct is potentially mutagenic due to possible tautomeric equilibria between the N6-amino and N6-imino structures, it may represent an initiating lesion in MAB hepatocarcinogenesis. (26 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

13. DISTRIBUTION OF LANGERHANS CELLS IN NORMAL AND CARCINOGEN-TREATED MUCOSA OF BUCCAL POUCHES OF HAMSTERS.

Schwartz J, Solt DB, Pappo J, Weichselbaum R
Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, 188 Longwood Ave., Boston, MA, 02115
J Dermatol Surg Oncol; 7(12):1005-1010 1981

The effect of 7,12-dimethylbenzanthracene (DMBA) applications on distribution of Langerhans cells was studied in the buccal mucosa of Syrian hamsters. After 5-wk exposure, the animals were sacrificed and the pouches were stained with ATPase. DMBA applications reduced the number and changed the morphology of Langerhans cells. The findings may indicate loss of immune function of Langerhans cells during chemical carcinogenesis. (17 Refs)

14. MORPHOLOGICAL CHANGES OF MYOFIBRIL IN THE CARCINOGENETIC COURSE OF 20-METHYLCHOLANTHRENE-INDUCED RHABDOMYOSARCOMA.

Hatakeyama S
Dept. Oral Pathology, Sch. Dentistry, Iwate Medical Univ., 19-1 Uchimaru, Morioka 020, Japan
Acta Pathol Jpn; 31(6):1029-1043 1981

In this study 20-methylcholanthrene (MC) was embedded in skeletal muscle tissue of mice. The resulting morphological changes were observed by light and electron microscope until the occurrence of rhabdomyosarcoma. The injected region of the muscle tissue in which MC was embedded went through three stages: destruction and degeneration, repair, and appearance of atypical cells. The morphologic figures of the myofibrils seen in the skeletal muscle cell during destruction and degeneration were similar to those observable in diseased human muscle, and were interpreted as nonspecific. The muscle tissue then regenerated in the same manner as seen during experimentally induced muscle tissue regeneration in both humans and animals. Abnormal mitotic figures were found 60 to 70 days after the injection of MC. Immature muscle cells, with tuft-formed myofibrils present, underwent abnormal mitosis in which one of the nuclei divided. The rhabdomyosarcoma cells produced by this abnormal mitosis began to appear in the lesion 70 days after the initial embedding of MC. The rhabdomyosarcoma cells in the induced tumor formed undifferentiated myofibrils in various degrees of maturation, and were therefore considered to play a part in the abnormal myofibrillar formation. (Author abstract) (28 Refs)

15. HAMSTER TONGUE CARCINOGENESIS. II. QUANTITATIVE MORPHOLOGIC ASPECTS OF PRENEOPLASTIC EPITHELIUM.

Eveson JW, MacDonald DG
Dept. Oral Medicine and Oral Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(5):332-341 1981

Morphologic features of ventral lingual mucosa were quantitated and compared using stereologic techniques in normal and 7,12-dimethylbenzanthracene (DMBA)-treated hamsters. Mucosa of 16 animals were scratched and treated with DMBA 3x/wk; mucosa of 8 controls were scratched and treated with acetone, and 8 other controls received no treatment. After 16 wk, scratch/acetone (S/A) control mucosa showed significant increases in epithelial and progenitor cell compartment thickness, number of progenitor cells, basement membrane length, and cells per unit of surface length. In relation to both untreated and S/A control mucosa, scratch/DMBA mucosa showed significant increases in mean total epithelial thickness, progenitor and keratinized cell compartment thickness, number and size of progenitor cells, basement membrane length, and progenitor cells per unit surface length. Although DMBA-treated maturation cells showed hypertrophy and hyperplasia, when compared with normal mucosa, there were no significant differences in size or number of maturation cells when compared with S/A control mucosa. Number of maturation cells per unit surface length in DMBA-treated mucosa was above normal but was not significantly different from that in S/A control mucosa. Application of similar techniques to human material could be useful in determining prognosis. (23 Refs)

16. A QUANTITATIVE STUDY OF LAMINA DENSA ALTERATIONS IN HAMSTER CHEEK POUCH CARCINOGENESIS.

White FH, Gohari K
Dept. Human Biology and Anatomy, Univ. Sheffield, Western Bank, Sheffield S10 2TN, England
J Pathol; 135(4):277-294 1981

Changes in the lamina densa (LD) of cheek pouch epithelium during carcinogenesis were studied in Syrian golden hamsters. Cheek pouches were painted with 0.5% 7,12-dimethylbenz(a)-anthracene 3x/wk for up to 15 wk. Five untreated hamsters served as controls. Tissue samples were examined by electron microscopy. Changes in the epithelium were classified according to histological criteria as hyperplasia, dysplasia, or carcinoma. Quantitative measurements were made using the index Ssld,bm, indicating the relative area of LD that was in normal relationship to the basal cell plasma membranes (BCM). Normal tissue had a lamina lucida (LL) of approx 300-400 nanometers in width separating the LD from the BCM. The width of the LL was fairly constant. Hyperplastic tissue showed occasional breaks in the LD and altered frequency and distribution of anchoring fibrils. Dysplastic tissue showed considerable variations in morphology, with cytoplasmic processes extending from the basal cells through breaks in the LD into the lamina propria. Carcinomatous tissue showed changes similar to those in dysplastic tissue, but to a greater extent. Ssld,bm was 98% for normal tissue, 88% for hyperplastic tissue, 76% for dysplastic tissue, and 42% for carcinomatous tissue. Findings indicate a progressive loss of LD during carcinogenesis. (71 Refs)

17. THE EFFECTS OF BENZO(A)PYRENE ON RAT LIVER LYSOSOMES.

Carevic M, Carevic O
Res. Centre Medicine and Psychology Traffic, Sarengradska 3, 41000 Zagreb, Yugoslavia
Toxicol Lett; 10(1):41-49 1982

Male and female rats receiving ip injections of benzo(a)pyrene (BP, 10 mg/kg) showed increased release of hepatic beta-glucuronidase, beta-galactosidase, and beta-N-acetylglucosaminidase, followed by increased activities of these enzymes in blood plasma. Lysosome-enriched liver suspension incubated for 20 min at 37 C with increasing concentrations of BP (10(-7), 10(-6), and 10(-5) M) exhibited no significant changes in specific activities of these enzymes. BP, at the same

three concentrations, caused increased release of the three enzymes during 20 min incubation in a concentration-dependent manner. Equal volume doses of dimethyl sulfoxide had no effect, or decreased release slightly. The observed lysosomal changes precede by several hours the onset of the altered cells or cell populations that appear in the liver approx 24 hr after BP administration. Injection of BP into rats may injure the lysolemma; injuries to the lysolemma may be an important feature of the early biochemical events in BP-initiated hepatocarcinogenesis. (29 Refs)

18. FURTHER CHARACTERIZATION OF THE EFFECTS OF 3-METHYLCHOLANTHRENE ADMINISTRATION UPON HEPATIC RIBONUCLEIC ACID POLYMERASE ACTIVITIES.

Liberator PA, Bresnick E
(c/o Bresnick) Vermont Regional Cancer Center, Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Chem Biol Interact; 38(1):53-73 1981

The administration of 3-methylcholanthrene (MC) to rats results in a marked increase in the specific activities of hepatic RNA polymerases I and II. In the present study, we were able to show that this increase was not caused by a shift in the ratio of 'free' to 'template-engaged' RNA polymerase. By means of binding studies with [3H]amatoxin, we were unable to demonstrate any increase in the number of RNA polymerase II molecules in liver after MC administration to the rats. RNA polymerase I was purified in excess of 3,000-fold from hepatic nuclei isolated both from control and MC-treated rats. The stimulation in activity was demonstrated at each step in the purification scheme until glycerol sedimentation analysis. Results from cation-exchange chromatography on phosphocellulose indicated that the polycyclic hydrocarbon increased the enzyme activity of RNA polymerase Ib somewhat specifically. Subsequent to glycerol gradient centrifugation, this stimulatory advantage was no longer evident. Reconstitution experiments revealed the presence of a stimulatory component, which was demonstrated in low mol wt fractions from both control and experimental preparations. (Author abstract) (47 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

19. INHIBITION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE- AND URETHAN-INDUCED LUNG TUMOR FORMATION IN A/J MICE BY LONG-TERM TREATMENT WITH DEHYDROEPIANDROSTERONE.

Schwartz AG, Tannen RH
Fels Res. Inst. and Dept. Microbiology, Temple Univ. Medical Sch., Philadelphia, PA, 19140
Carcinogenesis; 2(12):1335-1337 1981

Long-term treatment with the adrenal steroid dehydroepiandrosterone reduces weight gain without suppressing appetite and inhibits the occurrence of 7,12-dimethylbenz[a]anthracene- and urethan-induced lung tumors in A/J mice. (Author abstract) (26 Refs)

20. ENHANCED INHIBITION OF MAMMARY CARCINOGENESIS BY COMBINED TREATMENT WITH N-(4-HYDROXYPHENYL)RETINAMIDE AND OVARIECTOMY.

McCormick DL, Mehta RG, Thompson CA, Dinger N, Caldwell JA, Moon RC
Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicgo, IL, 60616
Cancer Res; 42(2):508-512 1982

Bilateral ovariectomy and dietary administration of the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR) are both effective inhibitors of chemical carcinogenesis in the rat mammary gland. The present study was designed to determine whether an enhanced inhibitory effect is obtained with combined ovariectomy and 4-HPR administration, compared to either treatment alone. In separate experiments, 50-day-old virgin female Sprague-Dawley rats received either a single iv injection of 50 mg N-methyl-N-nitrosourea per kg body wt or a single intragastric dose of 20 mg 7,12-dimethylbenz(a)anthracene. The experimental design was the same in both the N-methyl-N-nitrosourea and 7,12-dimethylbenz(a)anthracene experiments: Group 1, 25 intact rats, placebo diet; Group 2, 25 intact rats, supplement of 782 mg 4-HPR per kg diet; Group 3, 50 ovariectomized rats, placebo diet; Group 4, 50 ovariectomized rats, supplement of 782 mg 4-HPR per kg diet. Feeding of the 4-HPR supplement was begun 7 days after carcinogen administration; ovariectomy was performed 7 days post-7,12-dimethylbenz(a)anthracene or 14 days post-N-methyl-N-nitrosourea. In both experiments, combined ovariectomy plus 4-HPR was significantly more active in suppressing mammary cancer induction than was either manipulation alone. 4-HPR was a more effective inhibitor of carcinogenesis in ovariectomized rats than in intact animals. These data indicate that 4-HPR is highly effective in inhibiting ovarian hormone-independent cancers and suggest that retinoid inhibition of mammary carcinogenesis does not involve an influence on ovarian hormone action. (Author abstract) (19 Refs)

21. MODIFICATION OF MAMMARY CARCINOGENESIS AND TISSUE PEROXIDATION BY SELENIUM DEFICIENCY AND DIETARY FAT.

Ip C
Dept. Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY
Nutr Cancer; 2(3):136-142 1981

The independence of selenium (Se) and unsaturated fat intake as modifiers of the incidence of mammary tumors induced by 7,12-dimethylbenz(a)anthracene (DMBA) and the liability of mammary tissue to lipid peroxidation were studied. Female Sprague-Dawley rats were fed one of six synthetic diets (three different types of diets with and without Se supplementation) from weaning until termination of the experiment. The three basal diets contained different levels of tocopherol-stripped corn oil, 1%, 5%, and 25%. Mammary tumors were induced by intragastric administration of a 5 mg dose of DMBA at 50 days of age. Measurement of Se-dependent glutathione peroxidase activity in the rat liver was used to determine the functional status of Se at 0, 10, 20, and 30 days after the rats were given either the basal Se-deficient diet or the supplemented regimen. In rats receiving an adequate supplement of Se (0.1 ppm) tumor incidence increased proportional to the amount of corn oil in the diet. A deficiency of Se in the diet resulted in a marked enhancement in tumor incidence and yield in rats fed the 25% corn oil regimen. Glutathione peroxidase activity in the mammary gland was not influenced by dietary

fat but was severely depressed in the absence of added Se. Lipid peroxidation in the mammary tissue was elevated with increasing levels of dietary fat in rats supplemented with 0.1 ppm of Se. The unsupplemented 25% fat group showed significant enhancement of tissue peroxidation when compared to their supplemented controls. Determination of peroxide in the synthetic diets demonstrated that corn oil when mixed with the other ingredients, auto-oxidized very quickly especially at room temperature. The amount of peroxide formed is proportional to the content of corn oil and to the length of storage. Se deprivation did not affect the tumor growth rate or the proliferation of malignant vs benign lesions. (40 Refs)

22. EFFECT OF LAMBDA CARRAGEENAN ON TUMOR FORMATION IN TWO STAGE CHEMICAL CARCINOGENESIS OF MOUSE SKIN (MEETING ABSTRACT).

Inoue T, Yoshimoto T, Shindo H, Ogura T, Hirao F, Yamamura Y
3rd Department of Internal Medicine, Osaka University Medical School, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The dorsal skins of C57BL/6 male mice were initiated by 20 ug dimethylbenzanthracene (DMBA) at eleven wk old. Seven wk later, they were promoted by 2.5 ug 12-O-tetradecanoylphorbol-13-acetat e (TPA) twice weekly for 30 wk. One mg lambda-carrageenan was injected ip three x for a wk before initiation (group 1), before the beginning of promotion (group 2), or at the 7th wk of promotion (group 3). Mice in group 4 were not treated with lambda-carrageenan. The incidence of papilloma and the mean number of papillomas per mouse were reduced by lambda-carrageenan treatment. (no Refs)

23. CHEMICAL CARCINOGENESIS BY THE TWO-STAGE PROTOCOL IN THE SKIN OF MASTOMYS NATALENSIS (MURIDAE) USING TOPICAL INITIATION WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE AND TOPICAL PROMOTION WITH 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Wayss K, Reyes-Mayes D, Volm M
Deutsches Krebsforschungszentrum, Institut fur Exp. Pathologie, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Virchows Arch [Cell Pathol]; 38(1):13-21 1981

The long-term (34 wk) topical administration of 7,12-dimethylbenz(a)anthracene (DMBA) to the skin of male and female Mastomys induced a broad spectrum of benign and malignant tumors in all animals treated. In a two-stage carcinogenesis experiment with topical initiation with DMBA and topical promotion with 12-O-tetradecanoylphorbol-13-acetate (TPA), 50% of the animals developed both benign and malignant skin tumors. In general, benign tumors occurred between wk 15 and 25, whereas malignant tumors were seen 40 wk after initiation. In contrast to the situation in Mus musculus, the benign tumors consisted mainly of keratoacanthomas instead of fibroepitheliomas. In the non-initiated, TPA-treated, control group four benign and four malignant tumors were seen, whereas animals of the DMBA-initiated, acetone-treated control group were free of tumors. The promotion of virus transformed cells with TPA is discussed. (Author abstract) (36 Refs)

24. MUTAGENESIS IN FETAL RAT EPIDERMAL CELLS AND EFFECT OF TUMOR PROMOTER, 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (MEETING ABSTRACT).

Indo K, Miyaji H
Department of Pathology, Hyogo College of Medicine, Nishinomiya, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The effect of a tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on the frequency of mutation from 6-thioguanine (6TG) susceptibility to resistance of the aneuploid fetal rat epidermal cells by chemical carcinogens have been examined. Twenty-four hr treatment of wild type cells by 1 ug/ml dimethylbenzanthracene (DMBA) or 0.1 ug/ml N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG) induced 6TG mutants at the frequency of 49.4 x 10(-6) and 21.2 x 10(-6), respectively. The wild type cells totally died in the medium containing more than 0.1 ug/ml 6TG. However, carcinogen-induced 6TGr mutants showed 70% survival in the medium containing 1 ug/ml 6TG. Yield of 6TGr mutants was enhanced under the continuous existence of 10 ng/ ml TPA after carcinogen treatment. (no Refs)

25. EFFECT OF PHENOBARBITAL ON CHEMICALLY-INDUCED NEOPLASMS, MALFORMATIONS AND DOMINANT LETHALS IN MICE (MEETING ABSTRACT).

Gotoh H, Nomura T, Shibata K, Hata S, Enomoto T, Kusafuka T, Miyamoto S, Sakamoto Y
Department of Fundamental Radiology, Osaka University School of Medicine, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Phenobarbital (40-80 ug/g, sc) pretreatment of young adult and adult ICR/Jcl mice greatly diminished lung tumorigenesis initiated by urethane, furylfuramide (AF-2), and 7,12-dimethylbenz(a)anthracene (DMBA), while phenobarbital pretreatment enhanced embryo toxicities initiated by urethane, dimethyl-nitrosamine, 4-nitroquinoline-1-oxide, AF-2, and aminopyrine, but did not affect x-ray-induced ones. DMBA-induced dominant lethals were also enhanced by phenobarbital pretreatment. (no Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

26. A CLINICALLY RELEVANT CANINE LUNG CANCER MODEL.

Benfield JR, Shors EC, Hammond WG, Paladugu RR, Cohen AH, Jensen T, Fu PC, Pak HY, Teplitz RL, Thoms NW
Div. Surgery, City of Hope Medical Center, Duarte, CA, 91010
Ann Thorac Surg; 32(6):592-601 1981

Applicability of a dog model for the study of lung carcinogenesis was evaluated in 28 mongrel dogs and 74 beagle dogs. Animals were subjected to endobronchial submucosal injections or topical mucosal applications of carcinogens, implantation of Silastic discs that released carcinogens at a sustained rate, application of carcinogens to the epithelium of bistomal tracheal pedicle autografts, and endobronchial implantation of 91Y-emitting capsules. The following carcinogens were used: benzo(a)pyrene, nitrosomethylurea, 7,12-

dimethylbenz(a)anthracene, 3-methylcholanthrene, and 12-0-tetradecanoylphorbol-13-acetate. A total of 48 dogs survived long enough to be at risk for development of cancer. Endobronchial applications induced cancer in 17/56 lungs in 33 dogs at risk. In 14 dogs, 19 lungs remained at risk. Sustained-release implants induced 1 metastatic carcinoma in 42 lobes at risk in 15 dogs; 17 lobes in 11 dogs remained at risk. No lung cancers were detected in tracheal pedicle grafts. (19 Refs)

27. METHODOLOGY IN ESTABLISHING AN ANIMAL MODEL FOR LUNG CARCINOMA. I. LUNG CARCINOMA INDUCED BY INTRATRACHEAL INSTILLATION OF 3-METHYLCHOLANTHRENE SALINE SUSPENSION.

Tian H, Gao W, Liu M, Zuo R, Zhou D, Zou Z, Zhang H, Tang H
Dept. Pathology, Hubei Medical Coll., Wuhan, People's Republic of China

Zhonghua Zhongliu Zazhi; 3(2):94-96 1981

Results are described for a chemical carcinogenesis study of lung carcinoma in rats. A suspension of 3-methylcholanthrene (MCA) in sterile physiological saline and 0.2% gelatin cont aining 50 mg MCA/ml was instilled intratracheally in 162 white rats (81 each sex). The animals were divided into four groups: Group I and II were instilled with the carcinogen twice weekly while Group III and IV were instilled once weekly. Total treatments for Group I, II, III and IV were 2, 4, 5, and 7, respectively, with their respective total dosage of 10, 20, 25, and 35 mg. During 1-yr observation period, lung carcinoma was found in 126 animals, with tumor induction rates of 48.28% (13/27), 60.47% (25/41), 93.75% (14/14), and 92.5% (74/80) for Group I-IV, respectively, based on Ridit's statistical method. Except for two adenocarcinomas, all were squamous cell carcinomas, and only six were metastatic. Earliest tumor appearance was on day 34 after Group IV started the treatment. It was concluded that in rats, induction of lung carcinoma needed a five wk MCA instillation. (6 Refs) (In CHI)

28. HAMSTER TONGUE CARCINOGENESIS. I. CHARACTERISTICS OF THE EXPERIMENTAL MODEL.

Eveson JW, MacDonald DG
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England

J Oral Pathol; 10(5):322-331 1981

In an effort to develop a model of intra-oral carcinogenesis, 7,12-dimethylbenzanthracene (DMBA) was applied 3x/wk to ventral lingual mucosa of 20 hamsters. Each DMBA application was preceded by light scratching of the mucosa with a fine root-canal barbed broach. After 13 wk, 14/18 survivors had papillomas in the treated area and 12 tumors in the untreated floor of the mouth. Tumors were preceded by a phase resembling human leukoplakia. Biopsy specimens showed severe hyperplasia, hyperorthokeratosis, and variable degrees of dysplasia. Focal areas of acantholysis and dyskeratosis were observed, sometimes together. Squamous cell carcinomas showed a wide range of differentiation, sometimes within the same tumor mass. In control animals, oral mucosa that had been scratched and painted with acetone showed areas of white opacity and granularity, but no tumors. Macroscopic ulceration, which was not produced by the light scratching in this experiment, was not required for development of epithelial malignancy in DMBA-treated hamsters. (18 Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

29. USE OF THE IMPROVED ARABINOSE-RESISTANT ASSAY SYSTEM OF SALMONELLA TYPHIMURIUM FOR MUTAGENESIS TESTING.

Whong WZ, Stewart J, Ong TM
Div. Respiratory Disease Studies, National Inst. for Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV, 26505

Environ Mutagen; 3(1):95-99 1981

Improvement of the arabinose mutagenesis test system of Salmonella typhimurium by introducing an R factor plasmid (pKM101) into the testers is presented. Sensitivity of the R-factor plasmid containing tester strain S-50 and that of strain SV-21 was determined with three promutagens (2-aminoanth racene [2-AA], aflatoxin B1 [Afl B1], and benzo(a)pyrene [BaP]), three direct-acting mutagens (2-methoxy-6-chloro-9-[3(ethyl-2 chloroethyl)aminopropylamino]acridine x 2HCl [ICR-170], 2-methoxy-6-chloro-9-[3(2 chloroethyl)aminopropylamino]acridine x 2HCl [ICR-191], and methyl methanesulfonate [MMS]), and one air-sample oil shale ash extract (OSAE). The plate incorporation test with or without metabolic activation was used as the assay system. A weak or moderate mutagenic response to Afl B1, OSAE, and 2-AA and no response to MMS and BaP was observed in strain SV-21. High mutagenic response to all mutagens was noted in SV-50. With the R factor-containing strain (SVC-50), the mutagenic activity of Afl B1 can be detected at a dose of 10 nanog/plate. No mutagenic response to ICR-191 and weak mutagenic response to ICR-170 were observed with both strains when the standard selective medium was used. With addition of 0.2 mg glucose/plate in the selective medium, a substantial increase in sensitivity of both strains to the mutagens was observed. ICR-170 and ICR-191 were less mutagenic in SV-50 than SV-21. Results showed that addition of R factor plasmid (pKM101) substantially increases the mutagenic sensitivity of the tester to most mutagens tested, and that with tester SV-50, a simple plate incorporation test can be used in the arabinose mutagenicity system. (10 Refs)

30. METABOLIC ACTIVATION OF CARCINOGENS IN THE SALMONELLA MUTAGENICITY ASSAY BY HAMSTER AND RAT LIVER S-9 PREPARATIONS.

Raineri R, Poiley JA, Pienta RJ, Andrews AW
Chemical Carcinogenesis Program, Fredrick Cancer Res. Center, Frederick, MD, 21701

Environ Mutagen; 3(1):71-84 1981

In the Salmonella mutagenicity assay, mutagenicity of the known carcinogens 2-acetylaminofluorene (AAF), 2-aminoanthracene (AA), 3-methylcholanthrene (MCA), benzo(a)pyrene (BP), and diethylnitrosamine (DEN) were directly compared using either uninduced or phenobarbital (PB)- or Aroclor (AC)-induced liver S-9 preparations from both male and female hamsters and rats. Effects of different concentrations of the S-9 protein were studied. Mutagenicity data were compared with the aryl hydrocarbon hydroxylase (AHH) and BP-4,5-epoxide hydrase (EH) activities of the liver S-9 preparations, and the levels of binding of BP metabolites to DNA were measured. The preparations from hamster liver were consistently more effective than those from rat liver for the activation of AAF, AA (except for AC-induced preparations), MCA, and DEN to their mutagenic forms. Induced preparations from

rats were more active than those from hamsters when using BP. With the aromatic amines (AAF and AA), a partial inhibition of mutagenicity occurred at the highest protein concentrations tested. Inverse relationship was observed with BP between protein concentration and number of revertants occurring in the presence of the preparation from PB- and A C-induced male and female rats. Relative order of activities of AHH and EH in preparations was AC-induced greater than PB-induced greater than uninduced. An exception was the liver S-9 preparation from AC-induced female rats, which induced no EH activity. Levels of binding of the metabolites of tritiated BP to calf thymus DNA were correlated with AHH levels except in the case of the preparation from PB-induced female rats, in which no binding was detected. (31 Refs)

31. A 7-HYDROXYMETHYL SULFATE ESTER AS AN ACTIVE METABOLITE OF 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Watabe T, Ishizuka T, Isobe M, Ozawa N
Lab. Drug Metabolism and Toxicology, Dept. Hygienic Chemistry, Tokyo Coll. of Pharmacy, Horinouchi, Hachioji-shi, Tokyo 192-03, Japan
Science; 215(4531):403-405 1982

The compound 7-Hydroxymethyl-12-methylbenz[a]anthracene (7-HMBA), a carcinogenic major metabolite of 7,12-dimethylbenz[a]anthracene (DMBA) in liver, was transformed by liver cytosolic sulfotransferase to reactive 7-HMBA sulfate, which is mutagenic toward Salmonella typhimurium strain TA98. The mutagenicity of 7-HMBA in the presence of hepatic sulfotransferase was much higher than that of DMBA or 7-HMBA in the presence of hepatic monooxygenase. (Author abstract) (23 Refs)

32. SISTER CHROMATID EXCHANGE (SCE) INDUCTION BY PROMUTAGENS IN CULTURED HUMAN HEPATOMA CELLS (MEETING ABSTRACT).

Abe S, Sasaki M, Nemoto N
Chromosome Research Unit Fac Sci, Hokkaido University, Sapporo, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Cultured human hepatoma Hc-1 and Hc-4 cells were shown to produce an increased frequency of SCEs after treatment with benzo(a)pyrene (BP). Analysis of metabolism of BP by high pressure liquid chromatography indicated that Hc-1 and Hc-4 cells produce various kinds of BP metabolites including 7,8-dihydrodiol, a precursor of the ultimate metabolite of BP, which is supposedly responsible for induction of SCEs. Several other kinds of aromatic hydrocarbons, aflatoxin B1 and cyclophosphamide also induced SCEs in Hc-1 and Hc-4 cells. The findings suggest that Hc-1 and Hc-4 cells could convert a wide range of promutagens into active metabolites to induce SCEs, and may serve as simple in vitro screening systems for promutagens without exogenous activation systems. (no Refs)

33. IN VITRO EFFECT OF SOME MUTAGENS/CARCINOGENS ON CULTURED FISH CELLS.

Kocan RM, Landolt ML, Bond J, Benditt EP
Dept. Pathology SM-30, Univ. Washington, Seattle, WA, 98195
Arch Environ Contam Toxicol; 10(6):663-671 1981

Mutagenicity and toxicity of N-methyl-N'-nitro-nitrosoguanidine (MNNG) and benzo(a)pyrene (BP) were tested in cell line BF-2 derived from the bluegill sunfish (Lepomis macrochirus). Both MNN G and BP exposure resulted in production of ouabain-resistant mutant colonies. The mutation frequency after exposure to MNNG (direct mutagen) was greater than that after exposure to BP (promutagen). BP at 5 and 20 ug/ml produced dose-dependent decreases in cell number. Incubation of BF-2 cells with BP at greater than 5 ug/ml resulted in formation of intracellular crystals. (20 Refs)

34. CHEMICALLY-INDUCED UNSCHEDULED DNA SYNTHESIS IN PRIMARY RAT HEPATOCYTE CULTURES: A COMPARISON WITH BACTERIAL MUTAGENICITY USING 218 COMPOUNDS.

Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, Neal SB
Div. Toxicology, Lilly Res. Laboratories, Greenfield, IN, 46140
Environ Mutagen; 3(1):11-32 1981

Hepatocyte primary culture (HPC)-DNA repair test using a relatively large number of compounds representing a wide variety of chemical classes is discussed. Over 200 compounds were tested for induction of unscheduled DNA synthesis (UDS) and the results were correlated with bacterial mutagenicity using a modified Ames test. A positive response was seen in both systems with many procarcinogens and ultimate carcinogens while compounds believed to be noncarcinogens were inactive. Recognized carcinogens/mutagens were readily detected by the two systems. Structurally related noncarcinogens produced negative results in both systems. The modified Ames test and the HPC-UDS repair test were sensitive to compounds capable of interacting with DNA, and represent acceptable tests for genotoxic substances. The induction of UDS in hepatocytes showed good correlation with bacterial mutagenesis in response to polycyclic aromatic hydrocarbons, aromatic amines, biphenyls, nitrosamines, carbamates, azo-compounds, acridines, halogenated compounds, nitrosoureas, quinolines, pyridines, purines, pyrimidines, esters, and carbamates. Nitrocompounds although active in bacteria, were poor inducers of UDS. Results support the complementary and confirmatory nature of the tests for genotoxic chemicals and indicate the usefulness of the hepatocyte UDS system as a component in a battery of short-term predictive tests for mutagens/carcinogens. (45 Refs)

REVIEWS AND OTHER RELATED STUDIES

35. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.

Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

Fundamental research at the cellular and molecular levels on mechanisms of action of chemical carcinogenesis and applied aspects and the concept of 'molecular epidemiology' of cancer are reviewed. The action of initiating agents and their metabolism and covalent binding to macromolecules is discussed under the following headings: metabolic activation, carcinogen potency, structures of carc inogen-DNA adducts, conformational changes in DNA, carcinogen modification of mitochondrial DNA, DNA repair, and carcinogen-DNA modification and mechanism of initiation. Tumor promotion and multifactor interactions are discussed in relation to two-stage skin carcinogenesis. Numerous effects elicited by phorbol ester tumor promotors, particularly 12-O-tetradecanoyl-phorbol-13-acetate, are

classified into three categories: mimicry of transformation, modulation of differentiation, and membrane effects. Also considered in relation to phorbol ester tumor promotors, tumor promotion, and multifactor interactions are phorboid receptors, ion flux, possible role of kinases, chromosomal effects and activated oxygen, and chemical-viral interactions. The tumor-promoting activity of polycyclic aromatic hydrocarbons is discussed. A unified theory of tumor initiation and promotion is presented. Molecular epidemiology and cancer prevention are discussed with regard to limitations of current approaches and molecular cancer epidemiology. (94 Refs)

36. HEALTH EFFECTS OF COMBUSTION-GENERATED SOOT AND POLYCYCLIC AROMATIC HYDROCARBONS. PROGRESS REPORT, MAY 1, 1980-APRIL 30, 1981.

Thilly WG

Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA

Health Effects of Combustion-generated Soot and Polycyclic Aromatic Hydrocarbons. Progress Report, May 1, 1980-April 30, 1981. Available from National Technical Information Service, Springfield, VA, as DE81025651:, 54 pp., 1981.

Major progress has been made during 1980 in the development and conception of more useful human cell assays for genetic damage, in the identification of the major contributors to mutation of human cells by combustion effluents and in extending the use of the systems previously developed to the study of the mechanisms of chemical mutation of human cells. (Author abstract)

37. CARCINOGENESIS OCCURRING NATURALLY IN FOOD.

Hilker DM

Dept. Food Sciences and Human Nutrition, Univ. Hawaii, Henke Hall 224, 1800 East-West Road, Honolulu, HI, 96822

Nutr Cancer; 2(4):217-223 1981

The role of carcinogens which are metabolites of microorganisms infecting plants during harvesting and storage, products of the normal metabolism of plants, products of chemical changes occurring during processing, preservation, or preparation, and which are picked up from the environment through contaminated water or soil is discussed. Some of the most potent carcinogens are fungal metabolites such as aflatoxin B1, 4-ipomeanol, luteoskyrin, methylhydrazine, and ethylcarbamate. The pyrrolizidine alkaloids safrol, oil of calamus, cycasin, thiourea, and tannin also have carcinogenic activity. Polycyclic hydrocarbons, particularly benzo(a)pyrene (BP), are commonly found in food. BP can be found in plant food, seafood, and in meats. Polycyclic hydrocarbons including BP are formed by smoking meat and fish. Epidemiological studies indicate the high incidence of gastric cancer in the areas of the world where smoked fish are common in diets. Vitamin A and certain of its analogues can prevent the carcinogenic activity of BP and some other polycyclic aromatic hydrocarbons. The role of vitamin A appears more important when one considers that the diets of people in areas with high incidence of gastric cancer are low in vitamin A. The interrelated effects of vitamin A-poor diets, consumption of carcinogenic hydrocarbons, and the incidence of cancer need further study. Information is also needed on the amount of carcinogenic chemicals an individual must consume in order to exhibit cancer and on the interrelated effects of other dietary constituents. (59 Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/119

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

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2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
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American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
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6. MALIGNANT MELANOMA.
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7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
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Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
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VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
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J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

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12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
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Saxen E
Suomen Syoparekisteri, Linnankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
In FIN

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. A PRELIMINARY STUDY OF POLYNUCLEAR AROMATIC HYDROCARBONS IN THE SYDNEY ATMOSPHERE.

Gerstel MD, Basden KS
Shell Refining (Australia) Ltd., Sydney, N. S. W. 2000, Australia
J Proc R Soc New South Wales; 114(1/2):7-16 1981

Atmospheric suspended particulate matter was collected over ten 24-hr periods in New South Wales, Kensington, and the presence of polymorphonuclear aromatic hydrocarbons was investigated. The results were compared with other published reports for Melbourne and some North American cites. Trends of benzo(a)pyrene content were reviewed. The rapidity of the method of analysis was discussed. (30 Refs)

2. MEASUREMENTS OF BENZO(A)PYRENE IN THE CITY OF BOMBAY FOR THE EVALUATION OF CARCINOGENIC RISK.

Mohan Rao AM, Rajagopalan R, Doshi MH, Vohra KG
Air Monitoring Section, Div. Radiological Protection, Bhabha Atomic Res. Centre, Bombay-400 085, India
Sci Total Environ; 22(2):105-113 1982

Dust load and benzo(a)pyrene (BP) concentrations in the air were measured in an urban, suburban, and rural region of Bombay to determine the suitability of the three locations for epidemiologic studies. Samples were collected over a 24-hr period, 6 days/wk. The highest BP concentrations were recorded at the urban location (Matunga); these ranged from 1.0 ug/1,000 cubic meters in April 1980 to 35.7 ug/1,000 cubic meters in February 1980. BP concentrations at the suburban location (Deonar) varied between 0.1 and 1.8 ug/1,000 cubic meters, and those at the rural location (Alibag) ranged from 0.01 to 1.95 ug/1,000 cubic meters. At the urban location, the concentration data for both BP and dust load followed a log-normal distribution. BP concentrations at the urban location were similar to those of urban areas of the United States. The three locations appear to be suitable for sustained data collection on environmental carcinogens for epidemiologic studies. (13 Refs)

3. OCCURRENCE OF POLYCYCLIC AROMATIC HYDROCARBONS IN MUNICIPAL SEWAGE SLUDGE ASHES.

Wszolek PC, Wachs T
Toxic Chemicals Lab., New York State Coll. Agriculture and Life Sciences, Cornell Univ., Ithaca, NY, 14853
Arch Environ Contam Toxicol; 11(1):69-72 1982

The total amounts of polycyclic aromatic hydrocarbons (PAH) found in normal ashes of sludge from four cities (two heavily, and two, nominally industrialized) were 0.1-1.0 ug/g. The ash with the highest PAH content also contained the widest variety of compounds and was from an industrial city. Overall, anthracene was the most prevalent PAH type, but its amount did not correlate with extent of industrialization. The industrial city with low PAH variety was the only one of the four to employ the re-incineration technique. (8 Refs)

4. BENZO(A)PYRENE CONCENTRATIONS IN SOMATIC AND GONAD TISSUES OF BAY MUSSELS, MYTILUS EDULIS.

Mix MC, Hemingway SJ, Schaffer RL
Dept. General Science, Oregon State Univ., Corvallis, OR, 97331
Bull Environ Contam Toxicol; 28(1):46-51 1982

Concentrations of benzo(a)pyrene (BAP), a known carcinogen, in the somatic and g onadal tissues of Mytilus edulis and their relationship to seasonal fluctuations were investigated. Mean BAP concentrations in whole mussels were 33.81 ug/kg, which was not significantly different from mean whole body concentrations over the past four years. Seasonal variation of BAP in the gonad and somatic tissue resulted in values ranging from 5-20% and 80-97%, respectively. Whole body BAP concentrations were significantly correlated with BAP concentrations in somatic tissue but not the gonads. M edulis shows promise as a biological monitor for evaluating levels of polynuclear aromatic hydrocarbons in marine ecosystems. (13 Refs)

5. TRANSPORT OF POLYCYCLIC AROMATIC HYDROCARBONS THROUGH A PARTLY URBANIZED RIVER BASIN.

Herrmann R
Lehrstuhl fur Hydrologie, Universitat Bayreuth, Postfach 3008, D-8580 Bayreuth, W. Germany
Water Air Soil Pollut; 16(4):445-467 1981

The relationship between polycyclic aromatic hydrocarbon (PAH) load, concentration, and runoff in an urban environment, and processes involved in the PAH contamination of rainwater, from first contact to river pollution, were studied. Results indicated the possibility of considerable PAH pollution of rivers from the overflowing of storm waters into urban river basins, circumventing sewage plants. Pollution of the water supply can be effectively prevented by use of filtration and flocculation processes. (28 Refs)

6. EVALUATION OF RELATIVE ENVIRONMENTAL HAZARDS FROM A COAL GASIFIER.

Gangwal SK, Cleland JG, Truesdale RS
Research Triangle Inst., Research Triangle Park, NC
Evaluation of Relative Environmental Hazards from a Coal Gasifier. Available from National Technical Information Service, Springfield, VA, as PB81-217648:, 108 pp., 1981.

The report gives results of an evaluation of relative environmental hazards from a laboratory-scale coal gasifier. Detailed chemical analyses of four effluent streams (gas, aqueous condensate, tar, and ash) were performed for more than 30 gasification runs on a variety of coals, from lignite to bituminous. It briefly describes the gasification reactor, the associated sampling and analysis system, problems encountered with analyses, and special techniques for analyzing complex samples. Relative environmental hazards were determined using the Multimedia Environmental Goals methodology. Toxicity and mutagenicity were assessed using bioassay data. More than 400 effluent stream constituents were identified. Environmentally, the most significant effluent stream is aqueous condensate, followed by tar, product gas, and ash. However, on an equivalent weight basis, the tar stream is more toxic and mutagenic than aqueous condensate. Polycyclic aromatic hydrocarbons and organic bases are the most mutagenic fractions of the tar. Coal pyrolysis and gasification at higher temperatures leads to reduced tar mutagenicity. The most environmentally significant constituents (by stream) are: (1) product gas-CO, benzene, H2S, and carbonyl sulfide; (2) aqueous condensate - phenol/cresols/xy-

lenols (PCX), NH3, sulfides, thiocyanates, CN, As, and chlorides; and (3) ash - As, Ni, Be and Se. (Author abstract)

7. THE PRESENCE OF AFLATOXIN AND SOME POLYCYCLIC AROMATIC HYDROCARBONS IN HUMAN FOODS.

Emerole GO, Uwaifo AO, Thabrew MI, Bababunmi EA
Biomembrane Res. Section, Dept. Biochemistry, Univ. Ibadan, Ibadan, Nigeria
Cancer Lett; 15(2):123-129 1982

Analysis of common food items sold in Nigerian markets demonstrated the presence of benzo(a)pyrene (BP) and benz(a)anthracene (BA) in all fish and meat samples and aflatoxin in the food crops and spices tested. The highest hydrocarbon levels were found in moonfish, which contained 7.5 ug/kg BA, and in smoked meat, which contained 15.5 ug/kg BA and 8.5 ug/kg BP. Manihot flour, millet, corn, and groundnuts contained 1.2-1.7 mg/kg aflatoxin, whereas rice contained only 0.04 mg/kg. Results are discussed in relation to the relatively high incidence of cancer in tropical Africa. (32 Refs)

8. DECREASED RATE OF BENZO(A)PYRENE-INDUCED SISTER CHROMATID EXCHANGE IN FIBROBLAST CULTURES FROM PATIENTS WITH LUNG CANCER.

Rudiger HW, Harder W, Maack P, Kohl FV, Schmidt-Preuss U
Dept. Medicine I, Univ. Hamburg, Martinistr. 52, D-2000 Hamburg 20, W. Germany
J Cancer Res Clin Oncol; 102(2):169-175 1981

Fibroblast cultures from 29 lung cancer patients including 9 familial cases and from 25 healthy controls were investigated. We studied the benzpyrene-induced sister chromatid exchange (SCE) following incubation in the presence of 150 nM benzo(a)pyrene and found spontaneously increased SCE values in the patients' cells but a reduced response to benzpyrene as compared to the control cultures. The benzpyrene-induced SCE was positivcly correlated with both benzpyrene metabolism and DNA adducts in normal control cells but not in the patients' cells. The ratio of benzpyrene DNA adducts and benzpyrene-induced rate of SCE calculated for the individual cell strains exhibited a bimodal distribution with patients' cells, but not with control cells. We speculate that the described differences between patients' and control fibroblasts might reflect a genetic predisposition to the development of lung cancer in about one half of the patients tested. (Author abstract) (10 Refs)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

9. VARIATION IN METABOLISM OF BENZO[A]PYRENE IN EPIDERMAL KERATINOCYTES AND DERMAL FIBROBLASTS OF HUMANS AND MICE.

Kuroki T, Hosomi J, Nemoto N
Dept. Pathobiochemical Cell Res., Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan
Gann Monogr Cancer Res; 27:59-71 1982

Metabolism of benzo[a]pyrene (BP) in human epidermal keratinocytes (HEK) from normal subjects was investigated. BP is metabolized by a substrate-inducible cytochrome P-448-linked mixed-function oxygenase or aryl hydrocarbon hydroxylase (AHH). AHH activity was assayed by measuring formation of 3-hydroxy-benzo[a]pyrene (3-hydroxy-BP) from BP after incubation in reaction mixture containing cell homogenate, NADPH, and magnesium ions. The av value of noninduced basal AHH in six cultures of HEK was 3.3 picomoles equivalent of 3-hydroxy-BP/mg protein/hr and varied between 1.2 and 4.4. The variation in BP metabolism was studied in pairs of cultures of HEK and dermal fibroblasts, each isolated from the same subject. Dermal fibroblasts metabolized BP to a lesser extent than HEK, with the av basal AHH activity of three samples being 1.4 picomoles/mg protein/hr, and the ratio of the induced level to basal level being 4-6. Total metabolism of BP was low in dermal cells: 20-30% of added BP was metabolized in 48 hr in dermal fibroblasts, while 90% was metabolized by HEK in 48 hr under the same conditions. When HEK were cocultured with V79 Chinese hamster cells in the presence of BP, mutation was induced only with epidermal cells were used as the activating layer. Dermal fibroblasts did not activate BP to a mutagenic form(s) in cocultured V79 cells. Mouse dermal fibroblasts can activate BP and produce mutation in cocultured V79 cells. HEK have lower activities of uracil diphosphate-glucuronyl transferase and sulfate transferase than rodent embryo cells. (45 Refs)

10. FUNGAL OXIDATION OF 3-METHYLCHOLANTHRENE: FORMATION OF PROXIMATE CARCINOGENIC METABOLITES OF 3-METHYLCHOLANTHRENE.

Cerniglia CE, Dodge RH, Gibson DT
Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AK, 72079
Chem Biol Interact; 38(2):161-173 1982

The filamentous fungus, Cunninghamella elegans, was found to metabolize the potent carcinogen, 3-methylcholanthrene (3-MC) to 1-hydroxy-3-MC, 2-hydroxy-3-MC, 1-keto-3-MC, 2-keto-3-MC and trans-9,10-dihydrodiols of 1-hydroxy-3-MC. In addition several unidentified derivates of 3-MC were found. The metabolites formed were separated by high pressure liquid chromatography (HPLC) and identified by comparison of retention times, absorbance, fluorescence and mass spectra with those of synthetic standards. Incubation of (+-)-1-hydroxy-3-MC and (+-)-2-hydroxy-3-MC with cells of C elegans indicated that 1-hydroxy-3-MC is metabolized to form diasteromerically related trans-9,10-dihydrodiols of 1-hydroxy-3-MC. Experiments with 3-[14C]MC showed that over a 48-hr period, 8.7% of the hydrocarbon was oxidized to organic solvent soluble metabolic products. Most of the metabolites were polar products, some of which co-chromatographed with trans-9,10-dihydrodiols of 1-hydroxy-3-MC. The results show that C elegans has the ability to oxidize 3-MC to metabolites that have been implicated as proximate carcinogenic forms of 3-MC in higher organisms. (Author abstract) (34 Refs)

11. KINETICS OF GLUCURONIDATION OF PHENOL-DERIVATIVES OF BENZO(A)PYRENE WITH RAT AND MOUSE LIVER MICROSOMES.

Nemoto N, Takayama S
Dept. Experimental Pathology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
Toxicol Lett; 10(1):75-79 1982

Male Wistar rats (100-125 g) and male C57BL/6 and DBA/2 mice (6 wk old) were injected ip with 3-methylcholanthrene (3-MC, 100 mg/kg), and liver microsomal uridine diphosphate-

glucuronyl transferase was assayed by the method of Nemoto and Gelboin. Studies of the kinetics of glucuronidation with 3-hydroxybenzo(a)pyrene and 9-hydroxybenzo(a)pyrene reveal two apparent Km values for both compounds in both species. Km values were somewhat higher in liver microsomes of 3-MC-treated rats and mice than in the controls; the detergent Brij 58 (0.0125 %) also increased activities. The critical concentration of substrate was 2.5 uM for rats and 6.25 uM for mice. The transferase reaction is evidently either inhibited by concentrations above these amounts or activated by concentrations below them. (11 Refs)

12. STEREOSELECTIVE METABOLISM OF THE OPTICAL ISOMERS OF TRANS-1,2-DIHYDROXY-1,2-DIHYDROPHENANTHRENE TO BAY-REGION DIOL EPOXIDES BY RAT LIVER MICROSOMES.

Vyas KP, Thakker DR, Levin W, Yagi H, Conney AH, Jerina DM
Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Metabolism and Diseases, NIH, Bethesda, MD, 20205
Chem Biol Interact; 38(2):203-213 1982

Enantiomerically pure isomers of trans-1,2-dihydroxy-1,2-dihydrophenanthrene have been obtained by chromatographic separation of their diastereomeric bis esters with (-)-alpha-methoxy-alpha-trifluoromethylphenylacetic acid. Liver microsomes from control rats, as well as rats treated with phenobarbital or 3-methylcholanthrene, metabolize these dihydrodiols to a pair of diastereomerically related bay-region 1,2-diol-3,4-expoxides in which the benzylic hydroxyl group and the epoxide oxygen are either cis (isomer-1) or trans (isomer-2) to each other. In general, diol epoxide-1 was the major metabolite of the (+)-(1S,2S)-dihydrodiol, whereas diol epoxide-2 was the major metabolite of the (-)-(1R-2R)-dihydrodiol. The extent of this stereoselectivity is dependent on the source of the microsomes and is greatest for liver microsomes from 3-methylcholanthrene-treated rats; the ratio of diol epoxide-1 relative to diol epoxide-2 was 5.6 : 1 with the (+)-enantiomer as substrate and 1 : 5.5 with the (-)-enantiomer as substrate. For a given microsomal preparation, rates of metabolism were independent of the enantiomer composition of the substrate. Relative to microsomes from control animals, treatment of rats with 3-methylcholanthrene enhanced rates of metabolism by about 40%, whereas treatment with phenobarbital decreased rates to a similar extent when the amounts of metabolites formed per n anomole of cytochrome P-450 were compared. The failure of treatment by 3-methylcholanthrene to enhance markedly the rate of metabolism of a polycyclic aromatic hydrocarbon substrate is unusual. (Author abstract) (16 Refs)

BINDING TO CELLULAR MACROMOLECULES

13. THE AH REGULATORY GENE PRODUCT, SURVEY OF NINETEEN POLYCYLIC AROMATIC COMPOUNDS' AND FIFTEEN BENZO(A)PYRENE METABOLITES' CAPACITY TO BIND TO THE CYTOSOLIC RECEPTOR.

Bigelow SW, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
Toxicol Lett; 10(1):109-118 1982

The capacity of 19 polycyclic aromatic compounds and 15 benzo(a)pyrene metabolites to displace [1,6-3H]-2,3,7,8-tetrachlorodibenzo-p-dioxine (3HTCDD) from a hepatic cytosol Ah receptor from C57BL/6N mice was measured by scintillation spectrometry, after removal of the unbound TCDD by dextran-coated charcoal and sucrose density gradient centrifugation of the remaining sample. TCDD, dibenzo(a,h)anthracene, dibenzo(a,c)anthracene, benzo(a)pyrene, and 3-methylcholanthrene were the most effective in displacement of 3HTCDD from the Ah receptor. There was good agreement between these results and previously published studies on induction of monooxygenase activities. The capacity of Hepa-1 cells to metabolize polycyclic aromatic compounds was approx (lowest to highest): TCDD less than benzo(e)pyrene less than benzo(a)anthracene less than 3-methylcholanthrene approx = dibenzo(a,h)anthracene, which has no relationship to the rankings of these compounds as displacers of 3HTCDD. For all 15 benzo(a)pyrene metabolites examined, these was generally a correlation between percent displacement of 3HTCDD from the Ah receptor and fold induction of aryl hydrocarbon hydroxylase (AHH) activity. For all the compounds tested there is a good correlation between the displacement of 3HTCDD from the Ah receptor and the capacity to induce AHH activity, azo dye N-demethylase activity, or zoxazolamine metabolism. (36 Refs)

14. INFLUENCE OF COENZYME A ON THE IN VITRO BINDING OF BENZO(A)PYRENE METABOLITES TO PROTEIN.

Raha CR, Gallagher CH, Reeve VE
Eppley Inst. Res. in Cancer and Allied Diseases, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Res Commun Chem Pathol Pharmacol; 35(2):329-332 1982

Incubation of 20,000 x g supernatants of liver homogenates from female Wistar rats with benzo(a)pyrene (BP) and other cofactors in the presence of coenzyme A (CoA) produced metabolites that required extensive hydrolysis successively in 2N NaOH, 2N HCl, 2n NaOH and 6N HCl for their release. It is suggested that coenzyme A activated benzpyrenyl-amino acid formed via epoxide(s). The activated amino acid(s) became bound to thiol protein. (Author abstract) (6 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

15. EFFECTS OF 3-METHYLCHOLANTHRENE, BETA-NAPHTHOFLAVONE, AND PHENOBARBITAL ON THE 3-METHYLCHOLANTHRENE-INDUCIBLE ISOZYME OF CYTOCHROME P-450 WITHIN CENTRILOBULAR, MIDZONAL, AND PERIPORTAL HEPATOCYTES.

Baron J, Redick JA, Guengerich FP
Dept. Pharmacology, Toxicology Center, Coll. Medicine, Univ. Iowa, Iowa City, IA, 52242
J Biol Chem; 257(2):953-957 1982

Rabbit antiserum produced against cytochrome P-450 MC-B, the major isozyme of cytochrome P-450 isolated from hepatic microsomes of 3-methylcholanthrene-pretreated rats, was utilized in unlabeled antibody peroxidase-antiperoxidase and indirect fluorescent antibody staining techniques to investigate the effects of 3-methylcholanthrene, beta-naphthoflavone, and phenobarbital on the hemeprotein within centrilobular, midzonal, and periportal hepatocytes in livers of male rats. In livers of untreated and vehicle-pretreated rats, midzonal and periportal

hepatocytes were found to bind the anti-cytochrome P-450 MC-B to equal extents while centrilobular hepatocytes bound approximately 25% more antibody. Pretreatment of rats with phenobarbital did not result in alterations in either the intensity or pattern of immunohistochemical staining for cytochrome P-450 MC-B within the liver lobule. In livers of rats which had been pretreated with 3-methylcholanthrene, microfluorometric analyses revealed that the extent of anti-cytochrome P-450 MC-B binding increased by approximately 215% within both the midzonal and periportal regions of the lobule and by approximately 150% within centrilobular regions. Pretreatment of rats with beta-naphthoflavone resulted in alterations in the hemeprotein which were similar to those produced by 3-methylcholanthrene. Thus, after rats had been pretreated with either 3-methylcholanthrene or beta-naphthoflavone, the pattern of intralobular distribution of cytochrome P-450 MC-B was altered so that the antibody bound to approximately equal extents to hepatocytes within the three regions of the lobule. These results demonstrate that 3-methylcholanthrene and beta-naphthoflavone exert similar inductive effects on cytochrome P-450 MC-B within the liver lobule, with the least degree of induction of the hemeprotein being produced within centrilobular hepatocytes. (Author abstract) (42 Refs)

16. EXPRESSION OF AROMATIC POLYCYCLIC HYDROCARBON-INDUCED MONOOXYGENASE (ARYL HYDROCARBON HYDROXYLASE) IN MAN X MOUSE HYBRIDS IS ASSOCIATED WITH HUMAN CHROMOSOME 2.

Wiebel FJ, Hlavica P, Grzeschik KH
Institut fur Toxikologie u. Biochemie, Gesellschaft fur Strahlen-u. Umweltforschung, D-8042 Neuherberg-Munchen, W. Germany
Hum Genet; 59(4):277-280 1981

Mouse (BALB/cd) RAG cells, an established heteroploid cell line derived from renal adenocarcinoma, were fused with human fibroblast cell lines. Polycyclic aromatic hydrocarbon (PAH)-inducibl e monoxygenase (AHH: aryl hydrocarbon hydroxylase) activity toward benzo(a)pyrene and NADPH-cytochrome C (P-450) reductase activity were assayed. Uninduced AHH activities were undetectable or very low; induction of AHH with benz(a)anthracene (BA) alone, and especially with BA + aminophylline, increased activity substantially without changing the fluorescence spectra of the products. Preparations of RAG cells were apparently able to support oxygenation of benzo(a)pyrene by cytochrome P-448 to the same extent as with purified cytochrome c reductase. Presence of AHH activity in hybrid lines suggests that the structural gene of PAH-inducible monoxygenase or the gene(s) involved in enzyme induction are on human chromosome 2. However, a role for the mouse genes in expression of induced AHH cannot be ruled out. (32 Refs)

17. ONTOGENETIC VARIATION IN RAT LIVER, LUNG AND KIDNEY MONOOXYGENASE INDUCTION BY LOW DOSES OF BENZO(A)PYRENE AND CIGARETTE-SMOKE CONDENSATE.

van Cantfort J, Gielen JE
(c/o Gielen) Laboratoire de Chimie Medicale, Institut de Pathologie, Universite de Liege, Batiment B 23, Belgium
Br J Cancer; 44(6):902-910 1981

The specific lung-AHH induction, which we previously observed after the inhalation of cigarette smoke, is not due to the route followed by the inhaled smoke, for the same phenomenon occurs after ip injection of either cigarette smoke condensate (CSC) or benzo(a)pyrene in low doses. In this respect lung AHH behaves completely differently from the liver and kidney enzyme, in which organs, basal AHH activity (which is low in the fetus) increases rapidly after birth to reach the adult level 2 mo later, and is only inducible by CSC and low doses of BP in unweaned rats. In the lung, the basal AHH activity (low in the fetus) increases abruptly at birth, peaks in 5-day-old rats and then decreases slightly. Contrary to enzyme activity in other tissues, lung AHH cannot be induced in unweaned young animals. The enzyme subsequently becomes sensitive to inducing agents and is highly inducible in 90-day-old rats. Similar behavior occurs in two other enzymes linked to cytochrome P1450: ethoxycoumarin deethylase and ethoxyresorufin deethylase. The results could be related to the particular susceptibility of the lung to develop cancer after the inhalation of cigarette smoke. (Author abstract) (38 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

18. SYNERGISTIC EFFECTS OF INDIVIDUAL POLYCYCLIC AROMATIC HYDROCARBONS ON THE MUTAGENICITY OF THEIR MIXTURES.

Hermann M
Direction de Recherche, Environnement et Biologie Petroliere, Institut Francais du Petrole, B.P. 311, 92506 Rueil-Malmaison, France
Mutat Res; 90(4):399-409 1981

Enhancement and inhibition of mutagenic activity (MA) of benzo[a]pyrene (B[a]P) by polycyclic aromatic hydrocarbons (PAH) was studied in Salmonella typhimurium strain TA98. S9 mix pre pared from livers of Sprague-Dawley rats treated with Aroclor was used for metabolic activation. In the Ames assay bacterial cultures were exposed to B[a]P (0.5-3.0 ug/plate) with or without various PAH (less than or equal to 2,000 nanomoles/plate). Results obtained with PAH of 2-5 rings showed that all PAH tested enhanced MA of B[a]P. Naphthacene and benzo[e]pyrene enhanced MA of B[a]P at low concentrations but inhibited MA at higher concentrations. Neither naphthalene nor anthracene inhibited MA of B[a]P. Results indicate that the amount of PAH required for enhancement and inhibition effects decreases with increasing number of rings in the PAH structure. Several compounds with four rings, such as chrysene, pyrene, fluoranthene, and triphenylene, were exceptions to this rule. The effects of compounds with five or more rings were difficult to interpret because their own mutagenicity interfered with the synergistic effect on B[a]P mutagenicity, and inhibitory effects were evident in every case. Synergistic effects are apparently dependent on the spatial geometry rather than on specific properties of the PAH. PAH did not increase MA of benzo[a]pyrene-4,5-oxide, a direct-acting metabolite of B[a]P. Since B[a]P requires metabolic activation for MA, the result suggests that PAH exert synergistic effects at the level of enzymatic activation of B[a]P. (19 Refs)

19. DIESEL-EXHAUST-PARTICLE EXTRACT ENHANCEMENT OF CHEMICAL-INDUCED MUTAGENESIS IN CULTURED CHINESE HAMSTER OVARY CELLS: POSSIBLE INTERACTION OF DIESEL EXHAUST WITH ENVIRONMENTAL CARCINOGENS.

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Mutat Res; 103(3-6):349-355 1982

Dichloromethane extracts of exhaust particles (EP) filtered from the exhaust of diesel passenger cars of five different manufacturers were tested in combination with known mutagens using the Chinese hamster ovary (CHO) hypoxanthine-guanine phosphorylase assay. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5 ug/ml) and benzo(a)pyrene [B(a)P: 0.5 ug/ml] were administered with and without diesel EP extract (60 ug/ml in dimethyl sulfoxide) to CHO cells grown with and without Aroclor 1254-induced rat-liver S9 activator. Mutagenicity of the EP extract alone was uniformly low, but treatment of CHO cells with mutagen plus EP extract consistently yielded a mutant frequency higher than expected. Without S9 activation, combined treatment of EP -- MNNG gave a mutant frequency 1.4-1.9 x higher than expected. With S9 activation the EP + B(a)P treatments resulted in an observed mutation frequency 2.8-3.2 x the expected value. The observed enhancement phenomenon is highly reproducible, and also affects sister-chromatid exchanges and mutation to ouabain resistance. (21 Refs)

20. EFFECTS OF PHORBOL ESTERS ON FETAL RAT EPIDERMAL CELLS IN CULTURE.

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Gann Monogr Cancer Res; 27:145-158 1982

Effects of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on aneuploid nonmalignant fetal rat epidermal cells (FRSK-2 cells) were investigated. TPA inhibited cell proliferation at concentrations above 1 nanog/ml, while a stimulating effect was noted at concentrations of 0.01-0.1 nanog/ml after 24 hr. The inhibitory effect continued at 72 and 120 hr, while the stimulatory effect at low concentrations was not observed. TPA inhibited keratinization of lamellar processes of many aneuploid premalignant epidermal cell lines, but did not inhibit keratinization of malignant epidermal cell but destroyed the polarity retained in their keratinization processes. Two-stage treatment of FRSK-2 cells with benzo[a]pyrene (BP; 1 ug/ml for 1, 2, 7, or 14 days), then maintained in TPA-containing medium (1, 10, 100, and 1,000 nanog/ml) for 10 wk is reported. BP treatment for up to 2 wk did not induce any noticeable changes in the cells. However, BP treatment for 2 wk at 1 ug/ml resulted in stimulation of keratinization. TPA treatment severely inhibited the growth of FRSK-2 cells, even after BP treatment. Atypical cells were observed at 14-62 days after the beginning of TPA treatment. The changes induced in FRSK-2 cells by the two-stage treatment were irreversible. TPA treatment increased the plating efficiency of BP-treated cells. Following treatment with BP and TPA, the major characteristics of the cells included shortened generation time, acquisition of high plating efficiency values, and abnormal keratinization processes and growth on the agar surface, comparable with changes accompanying malignant transformation of fetal rat epidermal cells. (50 Refs)

21. REVERSAL OF THE PROMOTIONAL EFFECT OF 12-O-TETRA-DECANOYLPHORBOL-13-ACETATE ON MORPHOLOGICAL TRANSFORMATION OF HAMSTER EMBRYO CELLS BY GLUCOCORTICOIDS.

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Cancer Lett; 15(2):105-113 1982

Effects of glucocorticoids and cholesterol on morphologic transformation by benzo(a)pyrene (BP) and 12-O-tetradecanoylphorbol-13-acetate (TPA) in hamster embryo cells were studied. Cells exposed to BP (0.05 ug/ml) during the first 3 days of incubation (period 1) and then to TPA (0.05 ug/ml) during the last 3 days (period 2) had a transformation frequency of 10.2%. When present during period 2, hydrocortisone and dexamethasone strongly inhibited the formation of transformed colonies. Corticosterone had only a slight inhibitory activity and cortisone had no inhibitory activity when administered in concentrations up to 25 uM. Dexamethasone, the most potent glucocorticoid, reduced transformation frequency by greater than 50% at 0.25 nanoM and completely abolished transformation at 250 nanoM. Cholesterol (2.5 or 25 uM) increased transformation frequency. The glucocorticoids had no effect when present only during period 1. The fact that addition of dexamethasone (250 nanoM) reduced transformation frequency even when added 6 hr before staining suggested that glucocorticoids rapidly reverse the morphology of transformed colonies back to normal. (31 Refs)

22. DIFFERENTIAL EFFECTS OF DIETARY BHA ON HEPATIC ENZYME ACTIVITIES AND BENZO[A]PYRENE METABOLISM IN MALE AND FEMALE NMRI MICE.

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Carcinogenesis; 3(1):15-19 1982

The effect of dietary 2(3)-tert-butyl-4-hydroxy-anisole (BHA) alone and in combination with intraperitoneal injections of 3-methylcholanthrene (MC), on hepatic enzyme activities and benzo[a]pyrene (BP) metabolism was compared in male and female NMRI mice. In general, the characteristic induction pattern following dietary BHA administration in female mice could also be seen when male mice were used. The increase in epoxide hydrolase and cytosolic glutathione S-transferase following BHA feeding was however not as pronounced in males as in females. Also, MC treatment appeared to counteract the induction of GST activity by BHA in females but caused no such effect in males. Liver microsomes from untreated male mice catalyzed the metabolism of BP less efficiently than did microsomes from females. BHA treatment increased this activity in both sexes to a comparable extent and the overall activity was the same in males and females having received MC. The pattern of BP metabolites was altered following BHA treatment. In general, an increase in BP-4,5-diol and a decrease in 9-OH-BP was observed. This pattern was also noticed when microsomes from MC treated and MC + BHA treated animals were compared. MC treatment alone increased the amount of BP-7,8-diol, the quinones and the phenols. The present report indicates that several factors may contribute to the response to dietary BHA in mice. Whether this has any consequence in regard to this compound's anticarcinogenic effect remains to be elucidated. (Author abstract) (32 Refs)

23. INFLUENCE OF PREGNANCY AND LACTATION ON EXPERIMENTAL MAMMARY CARCINOGENESIS.

Moon RC, Shellabarger CJ, Henderson BE, Pike MC, Dao TL, Meites J, Sinha YN
Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616
Banbury Rep; 8:353-364 1981

The influence of pregnancy and lactation on experimental mammary carcinogenesis (MC) was studied in Sprague-Dawley female rats; 7,12-dimethylbenz(a)anthracene (DMBA)-induced MC in the rat is influenced by parity. The effect of age at which the first litter is borne on DMBA-induced MC, when MC is initiated at a subsequent period in the life of the animal, was examined. The age at which pregnancy ensues did not appear critical in the rat. Tumor hormone responsiveness in primiparous rats appears related to the age at which pregnancy occurs; pregnancy may alter the sensitivity of mammary cells to stimulatory hormones. (19 Refs)

24. DELAY IN HAMSTER BUCCAL POUCH CARCINOGENESIS BY ASPIRIN AND INDOMETHACIN.

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Oral Surg; 53(2):170-178 1982

Aspirin and indomethacin, administered systemically by oral route, were found to delay the development of hamster buccal pouch epidermoid carcinomas induced by thrice weekly topical applications of a 0.5% solution of 7,12-dimethylbenz(a)anthracene (DMBA) in mineral oil. Forty male and female Syrian hamsters (Mesocricetus auratus) were divided into four equal groups. In Group 1 animals the left buccal pouch was painted thrice weekly with DMBA. Group 2 animals were painted thrice weekly with DMBA and received 12 mg aspirin daily by oral route. Group 3 animals were painted thrice weekly with DMBA and received 1 mg indomethacin daily by oral route. Group 4 animals were maintained as untreated controls. Two animals in each of the four groups were killed with ether at 8, 10, 12, 13, and 14 wk after the start of the experiment. At the time of sacrifice the buccal pouches were photographed and the average number of tumors and the average size of tumors in each group were noted. The left and right buccal pouches were dissected, fixed in 10% formalin, sectioned in paraffin, and stained with hematoxylin and eosin. Autopsies were also performed on each animal. Both left and right buccal pouches and major organs were studied histologically. Both aspirin and indomethacin in the dosages used were found to delay DMBA buccal pouch carcinogenesis. A suggested mechanism of action is the inhibition of prostaglandin synthesis by the role of both aspirin and indomethacin as inhibitors of prostaglandin synthetase. Indomethacin appeared to exert a greater tumor-inhibiting effect than aspirin in the dosages used. (Author abstract) (25 Refs)

25. COMPARISON OF THE EFFECTS OF 3-ISOBUTYL-1-METHYLXANTHINE AND ADENOSINE CYCLIC 3':5'-MONOPHOSPHATE ON THE INDUCTION OF SKIN TUMORS BY THE INITIATION-PROMOTION PROTOCOL AND BY THE COMPLETE CARCINOGENESIS PROCESS.

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Carcinogenesis; 3(1):53-60 1982

Topical application of either 5 umol of 3-isobutyl-1-methylxanthine (IBMX) or 0.25 umol of adenosine cyclic 3':5'-monophosphate (cyclic AMP) to the initiated skin of the mouse prior to each promotion with 8.5 nmol of 12-O-tetradecanoylphorbol-13-acetate (TPA) inhibited the formation of papillomas and carcinomas. Combined treatments including IBMX and cyclic AMP caused additive reduction of the incidence of skin papillomas and carcinomas promoted by TPA. A good correlation was observed between the reduction of the tumor incidence by IBMX and cyclic AMP and their inhibition of TPA-stimulated polyamine, RNA, protein, and DNA synthesis. Since repeated treatments with these agents before or after initiation with a single subcarcinogenic dose of 7,12-dimethylbenz[a]anthracene (DMBA) did not alter significantly the development of skin tumors, the present results suggest that, in the two-step initiation-promotion protocol, both IBMX and cyclic AMP treatments may decrease specifically the promoting stimulus of skin carcinogenesis. The same doses of IBMX and cyclic AMP inhibited the accumulation of polyamines and the increase in macromolecular synthesis observed in DMBA-treated skin, but their effect on DMBA-induced skin carcinogenesis was dependent upon the protocol used and the dose of carcinogen applied. IBMX and cyclic AMP treatments failed to inhibit the induction of skin tumors by weekly applications of 0.2 umol of DMBA. In contrast to the inhibitor inhibitory effect of cyclic AMP treatment, IBMX enhanced the carcinogenic response to a single topical application of 3.6 umol of DMBA. The opposite effects of these agents on the carcinogenicity of DMBA correlated well with their different alteration of DMBA-induced unscheduled DNA synthesis in vitro. Cyclic AMP (0.5 mM) enhanced, whereas IBMX (0.5 mM) inhibited, the DMBA-induced incorporation of labeled precursor into DNA of isolated epidermal cells during incubation in the presence of hydroxyurea. Therefore, it is suggested that the different modulation of DMBA carcinogenesis by IBMX and cyclic AMP may result from concomitant effects on both the initiating and promoting components of the carcinogen. (Author abstract) (41 Refs)

26. TUMOUR INDUCTION BY CARCINOGENS IN IRON DEFICIENT RATS.

Webster DJ
Univ. Dept. Surgery, Welsh National Sch. Medicine, Heath Park, Cardiff, Wales
Anticancer Res; 1(5):293-294 1981

The hypothesis that a dietary iron deficiency state might influence the natural history of experimental animal tumors was tested. Results with dimethyl-benzanthracene-treated Wistar rats show a significant reduction in Hb levels but no difference in any of the parameters used to assess tumors. No spontaneous regression was seen. Results with 20-methylcholanthrene-treated animals revealed expected differences in Hb concentration but no other difference between treated and control animals. (14 Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

27. TUMOUR INITIATING ACTIVITY OF DIHYDRODIOLS OF BENZO(B]FLUORANTHENE, BENZO[J]FLUORANTHENE, AND BENZO[K]FLUORANTHENE.

LaVoie EJ, Amin S, Hecht SS, Furuya K, Hoffmann D
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 3(1):49-52 1982

The tumor initiating activities on mouse skin of benzo[b]fluoranthene, (B[b]F), benzo[j]fluoranthene (B[j]F), benzo[k]fluoranthene (B[k]F) and three of their dihydrodiols, 9,10-dihydro-9,10-dihydroxybenzo[b]fluoranthene (B[b]F-9,10-diol), 9,10-dihydro-9,10-dihydroxybenzo[j]fluoranthene (B[j]F-9,10-diol), and 8,9-dihydro-8,9-dihydroxybenzo[k]fluoranthene (B[k]F-8,9-diol) were evaluated. Among the parent hydrocarbons, B[b]F was the most potent tumor initiator, with activity greater than that of B[j]F but less than that of benzo[a]pyrene. B[k]F also showed tumor initiating activity, in contrast to its lack of complete carcinogenic activity on mouse skin. B[b]F-9,10-diol, which can form a bay region dihydrodiol epoxide, was as active as B[b]F. B[j]F 9,10-diol, which would form its dihydrodiol epoxide in a four sided pseudo-bay region was less active than B[j]F. B[j]F-8,9-diol was inactive. These results, together with parallel metabolic studies, suggest that the formation of bay region dihydrodiol epoxides may not be the major activation mechanism in benzofluoranthene tumorigenesis. (Author abstract) (25 Refs)

28. TWO-STAGE SKIN CARCINOGENESIS IN SENSITIVE AND RESISTANT MOUSE STRAINS.

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Carcinogenesis; 3(1):99-102 1982

Strains of laboratory mice vary markedly in their susceptibility to two-stage skin carcinogenesis using 7,12-dimethylbenz[a]anthracene (DMBA) as the initiating carcinogen and croton oil as promoter. This study has been undertaken in order to clarify the basis of the strain differences. LACA mice were used as the susceptible strain and BALB/c mice as the resistant strain. DMBA was a more effective complete carcinogen in LACA mice than in BALB/c mice. However, dose-response studies with respect to DMBA in the two strains in two-stage carcinogenesis suggested that metabolic activation of DMBA to the active carcinogen was not limiting in the resistant strain. The observed strain differences in response to DMBA in one and two stage carcinogenesis may reflect the ability of DMBA to also act as a promoter in the two strains. The possibility that the strains vary in their ability to repair damaged DNA has, however, not been eliminated. Unlike polycyclic aromatic hydrocarbon carcinogens such as DMBA, phorbol ester promoters (the active components in croton oil) do not appear to require metabolic activation. However, they are degraded and inactivated by epidermal and other cells. Experiments in which the dose and frequency of application of croton oil were increased, and the unrelated promoter anthralin was substituted for croton oil, failed to produce any evidence that differences in promoter degradation contributed to the differences in susceptibility between strains. (Author abstract) (12 Refs)

29. HAIRLESS MOUSE SKIN IN TWO-STAGE CHEMICAL CARCINOGENESIS. AN EXPERIMENTAL STUDY WITH SPECIAL REFERENCE TO CELL KINETICS, PAPILLOMA REGRESSION AND THE POSSIBLE DEVELOPMENT OF INCREASED CELLULAR RESISTANCE.

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Virchows Arch [Cell Pathol]; 38(3):263-272 1982

Hairless mice of the hr/hr Oslo strain were initiated by a topical skin application of 51.7 ug DMBA and thereafter treated by twice weekly applications of 17 nmol TPA. Papilloma development, the rate of papilloma regression and some cell kinetic parameters were studied. Papillomas were produced from wk 7 at an av rate of 0.33 tumors per animal per wk. This rate fluctuated from an initial rate of 0.33, which flattened off to 0.16 when TPA treatment was stopped for a period, and increased again to 0.34 when TPA applications were resumed. The treatment led to the development of hyperplasia, which was quantitated, and was most pronounced after 7 wk of promotion. Thereafter the hyperplasia dwindled. During TPA treatment a considerable reduction of epidermal turnover time was observed. After 8 wk of such treatment the turnover time of the epidermis was 24 h as compared with a normal time of 200 h. At the end of the treatment the turnover time increased again to about 50 h. Papilloma regression occurred frequently, but the rate at which this occurred slowed down after many wk of promotion. The mechanisms underlying regression are unknown, but are probably complex: a high cellular turnover rate, vascular catastrophes, scratching, fighting, eating by other animals and immune mechanisms may all be involved. Epidermal cells seem to develop increased resistance to the toxic effects of TPA during the treatment period. It is concluded that the skin of hairless mice reacts in the same way as that of sensitive mice with hair to the two-stage treatment protocol. (Author abstract) (24 Refs)

30. INVESTIGATION OF THE TUMORIGENIC RESPONSE TO BENZO(A)PYRENE IN AQUEOUS CAFFEINE SOLUTION APPLIED ORALLY TO SPRAGUE-DAWLEY RATS

Brune H, Deutsch-Wenzel RP, Habs M, Ivankovic S, Schmahl D
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J Cancer Res Clin Oncol; 102(2):153-157 1981

In a lifetime experiment benzo(a)pyrene (B(a)P) was administered to Sprague-Dawley rats either as an admixture to the diet or by gavage in an aqueous 1.5% caffeine soln. Dissolved benzo(a)pyrene induced more tumors of the forestomach than undissolved benzo(a)pyrene. The 1.5% caffeine soln (annual dose 27 g/kg) did not exert any carcinogenic activity under the conditions of this bioassay. (Author abstract) (17 Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

31. MUTAGENS IN DIESEL EXHAUST PARTICULATE: IDENTIFICATION AND DIRECT ACTIVITIES OF 6-NITROBENZO(A)PYRENE, 9-NITROANTHRACENE, 1-NITROPYRENE AND 5H PHENANTHRO(4,5-BCD)PYRAN-5-ONE.

Pitts JN, Lokensgard DM, Harger W, Fisher TS, Mejia V, Schuler JJ, Scorziell GM, Katzenstein YA

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Mutat Res; 103(3-6):241-249 1982

Combined chemical/microbiological analyses of diesel exhaust particulate organic matter (POM) are reported. Levels of three nitroarenes 1-nitropyrene (1NP), 9-nitroanthracene (9NA), and 6-nitrobenzo(a)pyrene (6NBP) were determined. A new type of direct mutagen in combustion-generated POM, 5H-phenanthro(4,5-bcd) pyran-5-one (IPAP) had been also determined. The base + neutral/(bn) fractions of dichloromethane (DCM) extracts of diesel exhaust POM were much more mutagenic than the acid fraction in the Ames test with Salmonella strains TA98 and TA98R, and the latter strain, a nitroreductase-deficient isolate of TA98, showed less response, indicating that direct activity of the bn fraction was due to nitro-substituted compounds. The presence of 1NP, 9NA, 6NBP, and IPAP in the bn fraction was confirmed by capillary gas chromatography/mass spectra analysis and other tests. Highly purified samples of the four compounds were compared using the Ames test with the standard mutagens quercetin, 2-nitrofluorene and benzo(a)pyrene, and the other mutagens (1 or 3) nitrobenzo(a)pyrene and (3 or 1) nitrobenzo(a)pyrene. 1NP accounted for 20 and 27% of the direct mutagenic activity exhibited by the total DCM extract and bn fraction, respectively. The compound accounts for about 50% of the 'nitroarene' portion of the direct activity, defined here as the difference between TA98 and TA98R responses, whereas 9NA and 6NBP make negligible contributions to the total activity. The activity of the lactone IPAP is reported here for the first time, and UV, fluorescence, and mass spectra data for the compound are given. (47 Refs)

32. MUTAGENICITY OF PARTICULATES IN SMALL ENGINE EXHAUST.

Ohnishi Y, Okazaki H, Wakisaka K, Kinouchi T, Kikuchi T, Furuya K

Dept. Bacteriology, Sch. Medicine, Univ. Tokushima, Tokushima 770, Japan

Mutat Res; 103(3-6):251-256 1982

Mutagenic activities of particulates in filtered exhaust from a small gasoline engine, a small diesel engine, and the new NiCE (Nippon Clean Engine Research Institute) thermo-atmosphere combustion gasoline engine were compared using the Ames test (strains TA98 and TA100; with and without S9). Generally the number of revertants in colonies treated with NiCE engine exhaust extracts was much lower than colonies treated with exhaust extracts of either the traditional gasoline engine or the small diesel engine. With a catalytic muffler emissions from the NiCE engine were markedly less mutagenic, no benzo(a)pyrene emissions were detected by high performance liquid chromatography of the muffled exhaust. (13 Refs)

33. MUTAGENIC CHARACTERIZATION OF SYNTHETIC FUEL MATERIALS BY THE AMES/SALMONELLA ASSAY SYSTEM.

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Mutat Res; 90(4):309-320 1981

Mutagenicity of solvent refined coal (SRC) distillates from two pilot processes (SRC-I and SRC-II) was studied in Salmonella typhimurium TA98. Samples tested included SRC-II heavy (HD), medium, and light distillates and SRC-I process solvent (PS), wash solvent, and light oil. HD and PS contained high-mol wt, high-boiling point compounds; of the crude samples only HD and PS showed mutagenic activity (MA). Dose-response curves were approx linear for HD and PS at 1-10 ug/plate. All MA required metabolic activation by S9 enzymes. Analysis of fractions of PS and HD obtained by solvent fractionation showed that specific MA was high for basic fractions, intermediate for basic tar and neutral tar fractions, and low for acidic tar fractions. Neutral, aliphatic, and neutral polyaromatic hydrocarbon-enriched fractions showed little or no MA. Fractions of PS obtained after solvent extraction accounted for 125% of the MA of crude PS; fractions of HD accounted for 88% of the MA of crude HD. Although the basic fractions of PS and HD had the highest specific MA, the basic tar and neutral tar fractions contributed the greatest portion of overall MA because these fractions made up 50% of the total weight of crude PS and HD compared with 1% of the basic fractions. The basic fractions of PS and HD had MA comparable to that of benzo[a]pyrene but less than that of 2-aminoanthracene. (25 Refs)

34. THE EFFECTS OF NITROUS ACID ON THE MUTAGENICITY OF TWO COAL LIQUIDS AND THEIR GENETICALLY ACTIVE CHEMICAL FRACTIONS.

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Mutat Res; 90(4):297-308 1981

The mutagenicity of solvent refined coal (SRC) distillates and distillate fractions was studied in Salmonella typhimurium TA98 and TA100 using the Ames assay. Chemicals tested included SRC-II heavy distillate (HD), SRC-I process solvent (PS), basic tar and neutral tar fractions of HD and PS, and samples of these chemicals that had been treated with either HCl or HNO2. SRC samples dissolved in dimethylsulfoxide or emulsified in HCl medium contained mutagens that required activation by S9 enzymes. Treatment of SRC samples with HNO2 reduced the observed mutagenicity. Mutagens detected after HNO2 treatment were direct acting; mutagenicity of the substances was apparently decreased by S9 enzymes. HCl did not decrease the mutagenicity of SRC samples. In the absence of S9 enzymes, mutagenicity of SRC compounds was reduced by 73% for PS, 80% for PS basic and neutral tars, and at least 90% for other SRC samples, compared with untreated samples. In the presence of S9 enzymes all HNO2-treated samples showed less than 10% of the mutagenicity of untreated samples. HNO2 treatment did not reduce mutagenicity of the non-primary aromatic amine polycyclic compounds phenanthridine, dimethylbenzacridine, benzo[a]pyrene, and 2-acetylaminofluorene. Results suggest that primary aromatic amines are the most important contributors to mutagenicity of SRC distillates in the Ames assay system. (21 Refs)

35. MUTAGENICITY AND CHEMICAL ANALYSIS OF ALIPHATIC AND AROMATIC FRACTIONS OF PRUDHOE BAY CRUDE OIL AND FUEL OIL NO. 2.

Ellenton JA, Hallett D.
Dept. of the Environment, Wildlife Toxicology Div., Natl. Wildlife Res. Center, Ottawa, Ontario K1A 0E7, Canada
J Toxicol Environ Health; 8(5/6):959-972 1981

Chemical analyses of aliphatic and aromatic fractions of Prudhoe Bay crude (PBC) oil and fuel oil number 2 and their potential mutagenicity were investigated. Fraction 1 of both oils exhibited no mutagenic activity. PBC oil fractions 3 and 4 and fuel oil number 2 fraction 4 produced weak mutagenic activity with metabolic activation. A significant increase in sister chromatid exchanges occurred after treatment with various concentrations of fraction 3 and 4 from each oil. These results indicate genetic activity residing in the polycyclic aromatic hydrocarbon containing fractions of the tested oils in both bacteria and mammalian cells. (20 Refs)

36. DETECTION OF CHEMICAL CARCINOGENS BY ASSAY OF UNSCHEDULED DNA SYNTHESIS IN RAT TRACHEAL EPITHELIUM IN SHORT-TERM ORGAN CULTURE.

Ide F, Ishikawa T, Takayama S
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J Cancer Res Clin Oncol; 102(2):115-126 1981

A short-term organ culture of rat tracheal epithelium was used to detect the ability of 53 chemicals to induce UDS. In this system all direct-acting compounds (ultimate or proximate carcinogens) tested induced UDS. Of 24 compounds requiring metabolism (procarcinogens), nine induced UDS, viz, 4NQO, AF-2, BP, DMN, DEN, and NP. Urethane, AAF, and 2,7-AAF induced very slight UDS. 3-Methyl-4NQO for which carcinogenicity data is incomplete was positive in our system. Among the cancer chemotherapeutic agents tested only mitomycin C induced UDS. MC and DMFA, which are known to induce cancer of respiratory organs in experimental animals, and DAB, aflatoxin B1 and Trp-P-1, which are strong carcinogens in the liver, did not induce UDS within 2 hr. With the longer exposure (24 hr), these carcinogens also failed to elicit UDS. All the carcinogens that induce UDS showed clear dose-dependent effects. No non-carcinogens tested induced UDS. These results suggested that this system should be useful for screening environmental chemicals suspected of damaging DNA of the respiratory organ on the basis of organotropic effects of UDS induction in cultured rat tracheal epithelium. (Author abstract) (54 Refs)

37. POTENTIAL IDENTIFICATION OF CHEMICAL CARCINOGENS IN A VIRAL TRANSFORMATION SYSTEM.

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(c/o Khoobyarian) Dept. Microbiology and Immunology, Sch. Basic Medical Sciences, Univ. Illinois at Medical Center, P.O. Box 6998, Chicago, IL, 60680
Chem Biol Interact; 38(2):253-265 1982

Chemical carcinogens from several diverse chemical classes ie; aromatic amines, polycyclic hydrocarbons, nitrosamines, hormonal derivatives, metals and direct alkylating agents cause a 5.2-50.5-fold increase in the frequency of murine sarcoma virus (MSV)-induced transformation in a normal rat kidney (NRK) cell system. Exogenous metabolic activation with a rat liver S-9 homogenate is required for expression of this activity by procarcinogens. Non-carcinogenic analogs of these compounds fail to cause significant increases in the transformation frequency either with or without prior metabolic activation. Iododeoxyuridine, a mutagen also does not cause enhancement of transformation. This system may serve as the basis for a rapid and quantifiable means of identifying chemical carcinogens while introducing a new model for the understanding of the interactions between oncornaviruses and chemical carcinogens. (Author abstract) (14 Refs)

38. HOST-MEDIATED MUTAGENESIS FOR DETECTION OF MUTAGENS/CARCINOGENS.

Ina N, Nishi Y
Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corporation, Nakogi 23, Hatano, Kanagawa 257, Japan
Gann Monogr Cancer Res, 27:73-84 1982

An in vivo-in vitro combination assay, host-mediated transplacental mutation assay (HTMA), has been established in which somatic cell mutations can be detected and measured quantitatively. Two genetic markers, 8-azaguanine resistance (8AGr) and 6-thioguanine resistance, were used for detection of forward mutations in fibroblasts of Syrian hamster embryos in pregnant mothers. Mutation frequencies increased linearly with increases in the dose of furylfuramide ip up to 100 mg/kg body wt of the mothers, when given ip or po; higher mutagenicity was observed following po administration than after ip treatment. Data obtained by HTMA on the effects of coadministration of secondary amines and nitrite, which result in formation of nitrosamines, are presented. Administration of morpholine plus sodium nitrite (500 mg/kg, each) markedly enhanced the mutagenic effect. Coadministration of aminopyrine and sodium nitrite had a more mutagenic effect on hamster embryonic cells than single administration of either compound alone. Thus, N-nitroso compounds produced in the body do cause gene mutations in embryonic tissues and organs. The induction of 8AGr mutations was studied in cultured cells from various organs of embryos of pregnant hamsters treated with benzopyrene (BP), nitrosodimethylamine (DMN), and N-nitrosoethylurea (NMU). Treatment with BP at 200 mg/kg produced more 8AGr mutations in embryonic lung cells than in kidney, liver, or brain cells. DMN (200 mg/kg) produced the highest frequency of 8AGr mutations in the embryo liver cells. After NME administration, there was marked increase in 8AGr mutations in brain cells. Detection of somatic mutations by HMTA is discussed. (45 Refs)

39. COMPARATIVE EVALUATION OF DIFFERENT PAIRS OF DNA REPAIR-DEFICIENT AND DNA REPAIR-PROFICIENT BACTERIAL TESTER STRAINS FOR RAPID DETECTION OF CHEMICAL MUTAGENS AND CARCINOGENS.

Suter W., Laeger I
Preclinical Res. Dept. Toxicology Unit, Sandoz Ltd., Basle, Switzerland
Mutat Res; 97(1):1-18 1982

Carcinogenic and noncarcinogenic compounds, including antibiotics, polycyclic aromatics, aromatic amines, alkyl halides, esters, epoxide carbamates and related compounds, nitroaromatics and heterocyclics, nitroso compounds, hydrazine compounds, azo compounds, and other bioactive agents, were tested for mutagenicity with the agar incorporation test (AT) and the spot test (ST). Two paired (DNA repair proficient/repair deficient) Bacillus subtilis systems, H17/M45 and HLL3g/HJ-15, were used, and the repair-proficient Escheri-

chia coli A1157 strain was paired with the repair-deficient strains JC2921, JC2926, JC5519, and JC5547. Results were compared with reported carcinogenicity and/or Ames test mutagenicity, or in some cases with Ames Salmonella (TA1535, TA1537, TA1538, TA98, TA100) assays reported here for the first time. E coli systems yielded a high number of 'no result' findings as well as many false-positive outcomes. B subtilis systems were generally reliable indicators of carcinogenicity, especially if both AT and ST were used. The bacterial DNA-repair tests agreed more often with the Ames test than with carcinogenicity results. When both pairs of B subtilis strains were combined with the Ames assay, excess false-positives did not appear, whereas the number of false-negative findings with carcinogens was reduced. The slightly increased probability of uncovering a suspected carcinogen does not seem to justify inclusion of the extra tests in a battery, except when working with chemicals of classes in which the Ames test is known to be less sensitive. (59 Refs)

40. POLYCYCLIC AROMATIC HYDROCARBONS AND POSSIBLE METABOLITES: CONVERTOGENIC ACTIVITY IN YEAST AND TUMOR INITIATING ACTIVITY IN MOUSE SKIN.

Siebert D, Marquardt H, Friesel H, Hecker E
(c/o Hecker) Institut fur Biochemie, Deutsches Krebsforschungszentrum, D-6900 Heidelberg, W. Germany
J Cancer Res Clin Oncol; 102(2):127-130 1981

The diploid respiratory-deficient strain of yeast D4-RDII was used to assay PAH and urethane as well as some oxygenated derivatives of PAH and the (aliphatic) epoxide hydrolase inhibitor TC PO for convertogenic (mutagenic) activity. As a positive control, the convertogenic ultimate rat liver carcinogen NOAcAAF was used. PAH and urethane were found inactive as convertogens, TCPO was weakly active, whereas oxygenated electrophilic derivatives of PAH, such as K-region oxides, were found strong convertogens. For comparison, some convertogenic key compounds were assayed for their tumor-initiating activity in mouse skin in the standardized system using TPA as a promoter. PAH were stronger initiators than all oxygenated derivatives of PAH tested. TCPO alone exhibited very weak, if any, initiating activity. It was unable to modify initiation to any significant extent, if administered 5 min prior to administration of an initiator. In the absence of correlation between convertogenic and initiating activity the question of the chemical nature of 'ultimate initiators' of mouse skin carcinogenesis awaits further investigation. (Author abstract) (35 Refs)

41. CYTOGENETIC EFFECTS ON THE EASTERN MUDMINNOW, UMBRA PYGMAEA, EXPOSED TO ETHYL METHANESULFONATE, BENZO[A]PYRENE, AND RIVER WATER.

Hooftman RN, Vink GJ
Organization for Industrial Res., TNO, P.O. Box 217, 2600 AE delft, Shoemakerstraat 97, The Netherlands
Ecotoxicol Environ Saf; 5(3):261-269 1981

The eastern minnow, Umbra pygmaea, was exposed to two known genotoxic agents and to water from the Rhine river at Lobith, The Netherlands. Both chromosome aberrations and sister chromatid exchanges (SCE) were scored. Fish were exposed to 0, 8, 40, and 200 mg ethylmethanesulfonate (EMS)/liter and 0, 10(-5), and 10(-4) mg benzo[a]pyrene (BaP)/liter at 20 C for 48 hr. Two additional groups of fish were exposed to 10(-4) mg/liter BaP for 4 and 6 days. EMS induced chromatid breaks, chromosome breaks, and gaps in gill and fin tissue; most of the aberrations were chromatid aberrations. EMS concentrations of 8, 40, and 200 mg/liter induced 1.1, 6.8, and 19.6% metaphases with aberrations, respectively. BaP only induced chromosome aberrations in fish exposed to the higher concentration; both chromatid breaks and gaps were seen. Activity of benzo[a]pyrene hydroxylase was near the detection limit (0.01 umole/g liver/hr). Bromodeoxyuridine injection to improve the number of metaphases with differential staining gave best results in gill tissue after two or three injections. Rhine water induced chromosome aberrations (chromatid breaks, chromosome breaks, gaps) and increased the number of SCE/metaphase. U pygmaea was suitable for detecting cytogenetic effects of chemical pollution in the aquatic environment. (18 Refs)

42. ROLE OF DNA REPAIR IN MUTAGENESIS OF CHINESE HAMSTER OVARY CELLS BY 7-BROMOMETHYLBENZ[A]ANTHRACENE.

Thompson LH, Brookman KW, Carrano AV, Dillehay LE
Biomedical Sciences Div., L-452, Lawrence Livermore Natl. Lab., P.O. Box 5507, Livermore, CA, 94550
Proc Natl Acad Sci USA; 79(2):534-538 1982

The role of DNA repair in mutagenesis was studied in normal, repair-proficient Chinese hamster ovary cells and in two mutant strains that are deficient in excision repair. By using the mutagen 7-bromomethylbenz[a]anthracene (7-BrMeBA) and the technique of alkaline elution of DNA, the mutants were found to be defective at or before the incision step of excision repair. Dose-responses were determined for cell killing, mutation induction at three loci, and sister chromatid exchanges over a survival range of 1.0-0.1 after 7-BrMeBA treatment. The mutants were five-fold more sensitive to killing than were the normal cells, but the degree of hypersensitivity to mutation induction varied depending on the mutant strain, the genetic marker, and the dose of mutagen. In each instance, the dose-response curve for mutations was essentially linear in the repair-deficient cells. In the normal cells, however, the curves for induced resistance to thioguanine and azaadenine were complex and were curvilinear with increasing slope at low doses. This behavior may be attributable to saturation of the excision repair system. No difference was seen in the efficiency of inducing ouabain-resistant mutations in the repair-deficient cells compared to the normal cells, indicating a qualitatively different behavior of this marker. These results are consistent with excision repair of 7-BrMeBA damage being error-free in Chinese hamster ovary cells. Sister chromatid exchange, another manifestation of DNA damage, also was induced with greater efficiency in the repair-deficient cells. (Author abstract) (34 Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

43. RELATIONSHIPS BETWEEN CARCINOGENICITY, MUTAGENICITY, AND THEORETICAL REACTIVITY INDICES FOR POLYCYCLIC AROMATIC HYDROCARBONS.

Seybold PG, Vestewig R, Scribner JD
Dept. Chemistry and Biological Chemistry, Wright State Univ., Dayton, OH, 45435
Int J Quantum Chem Quantum Biol Symp; 8:401-408 1981

Results of a quantitative statistical study of correlations between carcinogenic activity, mutagenic activity, and the theoretical indices for a sample of polycyclic aromatic hydrocarbons and some methyl derivatives are presented. An objective comparison with alternative techniques suggests a usefulness in cancer prescreening procedures of potentially hazardous substances. (42 Refs)

44. CARCINOGENICITY OF METHYLATED BENZO(A)PYRENE: CALCULATED EASE OF FORMATION OF THE BAY-REGION CARBONIUM ION.

Silverman BD
IBM Thomas J. Watson Res. Center, Yorktown Heights, NY, 10598
Cancer Biochem Biophys; 5(4):207-212 1981

The ease of carbonium ion formation in methylated benzo(a)pyrene (BP) was determined by calculating the difference in energy between diol-epoxide and triol-carbonium ion using two different molecular orbital programs. Substitution of a methyl group at either of the two positions adjacent to the benzo-ring, which becomes metabolized to the highly active diol-epoxide, induced changes that spanned the range of calculated reactivity. Substitution of a methyl group in the bay-region stabilized carbonium ion formation significantly The order of differences in bay-region diol-epoxide and triol-carbonium ion energies for the monomethyl BPs corresponded closely to reported relative carcinogenicities for the compounds. (20 Refs)

45. METHODS FOR THE RECOVERY OF ORGANIC CARCINOGENS FROM WATER.

Ehrlich K, Cawley G, Klein E
Gulf South Res. Inst., New Orleans, LA
Methods for the Recovery of Organic Carcinogens from Water. Available from National Technical Information Service, Springfield, VA, as PB81-209694, 41 pp., 1981.

The organic carcinogens benzo(a)pyrene, dieldrin, and N-acetyl-2-aminofluorene were recovered on XAD-2 macroreticular resin in yields of 90% or more from distilled water or seawater and in yields of 40% or more from lake Pontchartrain water containing a high concentration of organic material. The original solutions contained less than 500 parts per trillion of carcinogen. These results show that XAD-2 provides an efficient means for recovering nonpolar organic carcinogens from dilute solutions. More polar carcinogens such as dimethylnitrosamine were not effectively recovered on XAD-2 columns. Since XAD-2 binding would not be selective for carcinogens, the authors investigated methods which might bind carcinogens selectively from a mixture of organic compounds. We tested the ability of the above carcinogens to bind to nucleic acid using direct binding, equilibrium dialysis, nuclei binding, and binding to DNA-cellulose. Radio-labeled carcinogens were used to quantify the amount bound. Either rat liver nuclei (0.1 mg DNA) or DNA-cellulose (1 mg DNA) bound 18% of the acetylaminofluorene and up to 66% of the dieldrin from solutions containing 150 to 280 nmoles of compound. Up to 30% of the benzo(a)pyrene from solutions containing as much as 320 pmoles was bound. Tenfold or lower recoveries were found when direct-binding methods were used. (Author abstract)

46. CHARACTERIZATION OF POLYCYCLIC KETONES AND QUINONES IN DIESEL EMISSION PARTICULATES BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY.

Choudhury DR
Vick Div. Res. and Development, Richardson-Vicks Incorporated, 1 Bradford Road, Mount Vernon, NY, 10553
Environ Sci Technol; 16(2):102-106 1982

High-resolution gas chromatography/mass spectrometry was used to determine the chemical composition of two highly mutagenic subfractions of the neutral fraction of a diesel particulate extract. Diesel emission particulates were collected from a Volkswagon Rabbit by the dilution tunnel method and the two subfractions were isolated by silica gel chromatographic fractionation of the neutral extract. Of seven subfractions prepared, subfractions 4 and 5 had the highest specific mutagenicity in the Ames Salmonella mutagenesis assay, with subfraction 4 accounting for 52% of the direct-acting mutagenicity and subfraction 5, 13%. Both direct-acting mutagens and promutagens which required metabolic activation were found in the subfractions. Elution patterns suggested that the subfractions contained compounds more polar than parent and alkyl-substituted polycyclic aromatic hydrocarbons. Ketone, quinone, carboxaldehyde, and hydroxy derivatives and their alkyl homologues were characterized. The single largest family of compounds detected were 9-fluorenone and its C1-C4 alkyl homologues. The mutagenicity of most of the compounds identified is unknown. (18 Refs)

47. CORRELATION BETWEEN THE ASSOCIATION AND THE DESMUTAGENICITY OF BENZO(A)PYRENE BY HEMIN; COMPARISON WITH HEMOPROTEINS, TRANSIENT METALS AND AMINES.

Yagi M, Akagawa S
Dept. General Education (Physics Lab.), Tokyo Medical and Dental Univ., Ichikawa, Chiba, 272, Japan
Cancer Biochem Biophys; 5(3):175-181 1981

Benzo(a)pyrene (BP) binding was accomplished in methanol:H20 (3:1) for 10 min on thin-layer chromatography plates with the following compounds: beef hemin, beef methemoglobin, human oxyhemoglobin, beef liver catalase, p-phenylenediamine (pPDA), hydroxylamine, 3,3'-diaminodipropylamine (DADPA) cupric chloride, and ferric chloride. After binding, unbound BP was removed and its concentration determined by fluorescence in dimethyl sulfoxide soln. Association constants (Kass) of BP with hemin and other compounds were determined by an equation relating the difference between free and bound fluorescence intensities. Mutation assay was by a modified Ames method with Salmonella typhimurium strain TA100; a desmutagenicity constant (Kmut) was calculated by a similar difference method. The loss of mutagenicity of BP was caused by binding with materials containing ferric but not ferrous iron. Kass and Kmut were, respectively, 8.5 x 10(4) and 7.0 x 10(4) for hemin and 2.2 x 10(3) and 2.3 x 10(3) for DADPA. The respective figures for other compounds were both less than 1,000 (FeCL3, pPDA) or differed by a large amount (CuCl2, hydroxylamine). (20 Refs)

REVIEWS AND OTHER RELATED STUDIES

48. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.

Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

Lung interactions with aliphatic, alkylated aromatic, and polycyclic aromatic hydrocarbons are reviewed. Emphasis is placed on the metabolic mechanisms responsible for detrimental effects to the lungs following exposure to these compounds. Included in the discussion of aromatic hydrocarbons and the lungs are considerations of the effects of exposure to smoke and inducing agents, benzopyrene metabolism in perfused lungs, hydrocarbon metabolism as a test for identification of individuals predisposed to develop lung cancer, and hydrocarbon metabolism in human lungs. (163 Refs)

49. AROMATIC HYDROCARBONS: METABOLISM BY BACTERIA, FUNGI AND ALGAE.

Cerniglia CE
Natl. Center for Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079
Rev Biochem Toxicol; 3:321-361 1981

Microbial metabolism of aromatic hydrocarbons, including benzene, biphenyl, naphthalene, phenanthrene, anthracene, benzo(a)pyrene, and benz(a)anthracene, is reviewed. Enzymes involved in the microbial metabolism of aromatic hydrocarbons are described. The data demonstrates that bacteria, fungi, and algae have the enzymatic capacity to metabolize aromatic substrates that range in size from benzene to benzo(a)pyrene. It was also shown that fungi can metabolize polycyclic aromatic hydrocarbons to metabolites known to be carcinogenic, mutagenic, and acutely toxic to experimental animals. (153 Refs)

50. GASTROINTESTINAL CANCER: ENDOGENOUS FACTORS.

Bruce WR, Correa P, Lipkin M, Tannenbaum SR, Wilkins TD
Ontario Cancer Inst., Toronto, M4X 1K9, Canada
Banbury Rep 7: 468 pp., 1981.

The role of diet in cancer was examined. Sessions on gastrointestinal microbiology (microbiological considerations in experimental studies, effect of diet on human fecal flora, metabolism of xenobiotics by intestinal flora, and intestinal bacterial activity and carcinogenesis), fiber (ecology of gut fermentation in man, dietary fiber breakdown in the human colon role of fat, fiber, and other modifiers of intestinal carcinogenesis in cancer prevention), host response to carcinogens (risk factor profiles for individuals at increased risk for colon cancer, fecal mutagens and colorectal polyps, enzymes of normal, premalignant, and malignant colonic cells, role of cytochrome P-450 in colon response xenobiotics, inhibitors of gastrointestinal neoplasia, colonic activation of carcinogens), mutagens (in extracts of gastrointestinal mucosa, nitrosation in stomach mucosal tissue of humans and dogs, isolation of mutagens produced in the human colon by bacterial action, structural studies and properties of mutagens isolated from human feces, bacterial fluctuation tests of mutagenic activity in human feces, intake, formation, and release of mutagens by man), N-nitroso compounds (endogenous formation of N-nitroso compounds, analysis of human biological specimens for nitrosamines, block nitrosamine formation using ascorbic acid and alpha-tocopherol, distribution and metabolism of nitrate and nitrite in rats, analysis of nitrate, nitrite, and nitrosamines in human feces, metabolism of nitrate), bile acids and other lipids (bile salts as tumor promoters, bile acids in colorectal carcinogenesis, and analysis of feces for benzopyrene after consumption of charcoal-broiled beef) and epidemiology and design of future studies (epidemiologic tests of hypothesis relating diet and cancer, large-scale cohort study of diet and selected digestive system cancers, and possible application of mutagenesis testing to cancer epidemiology). (716 Refs)

51. DISCUSSION: COLONIC ACTIVATION OF CARCINOGENS.

Wogan GN, Montesano R, Goldin BR, Reddy BS, Magee PN, Archer MC, Goldman P, Balish E, Newmark H, Venitt S, Wattenberg LW, Strobel HW

Massachusetts Inst. Technology, Boston, MA
Banbury Rep; 7:167-172 1981

Experiments in rat colon explants exposed to benzo(a)pyrene (BP) suggest that the colon can fully activate this series of carcinogens by the same pathways as those observed in other tissues. A tissue's sensitivity to a carcinogen is related to its capacity to activate the carcinogen (although the site of metabolic activation is not necessarily the site of tumorigenesis) and its capacity to repair DNA damage induced by that chemical. To a certain extent, the known inhibitors of carcinogenesis can be divided into two groups. Some inhibitors cause 'phase 2' detoxification (essentially, conjugation) reactions; they alter the metabolism of the mixed function oxidase (MFO) system but do not increase its activity. In the case of BP, the effect of a 'phase 2'-active inhibitor is to reduce the formation of the ultimate carcinogen. The other inhibitors of carcinogenesis, for which beta-naphthoflavone is a prototype, caused both 'phase 1' and 'phase 2' reactions. MFO activity is enhanced. These agents simultaneously induce oxidative reactions (often leading to activation of the carcinogen) and enhanced detoxification reactions. The net result in most cases is protection of the host against the carcinogen. (8 Refs)

52. REVIEWS IN BIOCHEMICAL TOXICOLOGY.

Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

Topics discussed in relation to biochemical toxicology include the following: xenobiotic-metabolizing enzymes (identification and purification of multiple forms of uridine diphosphate-glucuronosyltransferase; organic sulfur substrates for the microsomal flavin-containing monooxygenase), biochemical toxicology of organs and organ systems (properties of distribution of enzymes of pulmonary cytochrome P-450-dependent monooxygenase systems; metabolic interactions of hydrocarbons with mammalian lung), toxic compounds (biochemical toxicology of benzene; metabolic activation and detoxification of aflatoxins), modes of toxic action (mechanisms of fibrosis and cellular and biochemical mechanisms of mouse skin tumor promoters), methodology of biochemical toxicology (use of model systems in biochemical toxicology: heme models), comparative toxicology (metabolism of aromatic hydrocarbons by bacteria, fungi, and algae). (1276 Refs)

53. INITIATION AND PROMOTION, MUTAGENESIS AND TRANSFORMATION OF C3H/10T1/2 MOUSE EMBRYO FIBROBLASTS.

Heidelberger C
Univ. Southern California Sch. Medicine, Los Angeles, CA, 90031
Gann Monogr Cancer Res; 27:207-219 1982

The C3H/10T1/2 mouse embryo fibroblast cloned cell line is discussed with respect to initiation and promotion, mutagenesis, and transformation. Transformation by polycyclic aromatic hydrocarbons was dose-dependent and did not involve activation of an endogenous retrovirus or its genes or RNA. Metabolism of benzo[a]pyrene in microsomes of these cells involves formation of 7,8-and 9,10-diols, phenols and quinones. UV light is a pure initiator, x-rays initiate transformation, and saccharin a weak promoter. While 12-O-tetradecanoyl phorbol-13-acetate (TPA) is strongly mitogenic and produces hyperplasia in mouse skin, it does not significantly increase the saturation density of C3H/10T1/2 cells. All chemical classes of tumor promoters are not suitable for screening by measuring their effects on the 5-azacytidine-induced differentiation of C3H/10T1/2 cells because of inconsistencies in results. Mutagenic and oncogenic transformation in these cells is described. Mutagenesis data can be interpreted in various ways in order to obtain the desired result. In this system mutagenesis appears to be necessary but is not sufficient for transformation. (60 Refs)

54. CARCINOGENIC EFFECTS OF COAL-CONVERSION MATERIALS.

Renne RA, Smith LG
Battelle Pacific Northwest Lab., Richland, WA
Carcinogenic Effects of Coal-Conversion Materials. Available from National Technical Information Service, Springfield, VA, as DE81028108:, 29 pp., 1981.

Tremendous expense and extensive time commitments are required for in vivo mammalian carcinogenesis tests. Regulatory agencies may not be completely satisfied without some repetition of the toxicity testing with the final product from the commercial plant. Nevertheless, I think the work that we are doing on these materials from the pilot and demo plants is valuable. We are attempting to determine the correlation between mutagenesis and carcinogenesis data on complex mixtures such as these synfuel materials. The heavy distillate that we are working with was highly mutagenic compared with the other materials tested in the Ames system; it was also highly carcinogenic in our mouse skin-painting assay. when we tested the fractions, we had somewhat different results from those of the mutagenesis assays: the basic fraction of the heavy distillate was highly mutagenic, but, at least now, it does not appear to be highly active in our mouse carcinogenesis assay. However, the basic tar and the neutral tar skin carcinogenesis data correlate fairly well with the mutagenesis data. The second point I would like to make is to emphasize the need for caution against depending heavily on equating PNA content with carcinogenic activity. I would like to point out that our data indicate that PNAs are not the only chemical group with which we should be concerned. We should also monitor for primary aromatic amines. Due to the concern inhalation of synfuels, we have begun inhalation studies on some of the SRC materials. (Author abstract)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lolman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

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NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
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3. CHEMICAL CARCINOGENESIS AND SMOKING
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Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(5):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York NY, 10032
J Supramol Struc. Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.
Hoffman DA, Felter RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.
Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-211 1981

7. DIET AND CANCER OF THE LARGE BOWEL.
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Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
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Polycyclic Aromatic Hydrocarbons and Related Compounds

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. STUDIES ON THE ENVIRONMENTALLY INDUCED CONTAMINATION OF FOODS WITH CANCERIGENIC HYDROCARBONS IN GDR AND IN HUNGARIAN PEOPLE'S REPUBLIC.

Fritz W, Soos K
Zentralinstitut fur Ernahrung, Arthur Scheunert-Allee 114-116, DDR-1505 Bergholz-Rehbrucke, E. Germany
Nahrung; 25(10):905-913 1981

Environmentally induced contamination of foods with cancerigenic hydrocarbons was measured by determination of benzo[a]pyrene (BaP) in food grown close and far away from industrial plants (IP) in German Democratic Republic (GDR) and in Hungarian People's Republic (HPR). BaP content of vegetables grown far away from IP in GDR was 0.01-2.3 ug/kg of fresh wt and in HPR was 0.05-3.85 ug/kg with av values of 0.43 ug/kg and 0.6 ug/kg, respectively. The BaP content of vegetables grown close to IP in GDR was 0.15-12.4 ug/kg, and in HPR was 0.05-19.6 ug/kg. In HPR values obtained near a new petrochemical plant were 3.5 times higher than values obtained far away from IP, but values obtained near an old petrochemical plant were 8 times higher. Degree of contamination depends very much on the type of industrial plant. Values obtained in GDR close to coking, tar extraction, or carbon black plants were 10-100 times higher. (30 Refs) (In GER)

2. EVALUATION OF RELATIVE ENVIRONMENTAL HAZARDS FROM A COAL GASIFIER.

Gangwal SK, Cleland JG, Truesdale RS
Res. Triangle Inst., Research Triangle Park, NC
Sci Tech Aerosp Rep; 19(24):3371 1981

Environmental hazards from a laboratory scale coal gasifier were evaluated. Relative environmental hazards were determined by the multimedia environmental goals methodology. Toxicity and mutagenicity were assessed. It is found that environmentally, the most significant effluent stream is aqueous condensate, followed by tar, product gas, and ash. However, on an equivalent wt basis, the tar stream is more toxic and mutagenic than aqueous condensate. Polycyclic aromatic hydrocarbons and organic bases are the most mutagenic fractions of the tar. Coal pyrolysis and gasification at higher temperatures leads to reduced tar mutagenicity. (Author abstract) (no Refs)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

3. METABOLISM OF BENZO[A]PYRENE BY GUINEA PIG ADRENAL AND HEPATIC MICROSOMES.

Colby HD, Johnson PB, Pope MR, Zalkoski JS
Dept. Physiology, West Virginia Univ. Sch. Medicine, Morgantown, WV, 26506
Biochem Pharmacol; 31(5):639-646 1982

Studies were carried out to compare the metabolism of benzo[a]pyrene (BP) by adrenal and hepatic microsomes obtained from adult male guinea pigs. Adrenal microsomes produced fluorescent metabolites (primarily phenols) approx three to four times more rapidly than hepatic microsomes, but the differences in the rates were considerably smaller when total BP metabolism was assessed using an isotopic assay. The apparent discrepancy between the two assays is attributable to differences in the profiles of BP metabolites produced by adrenal and liver. Separation of metabolites by high pressure liquid chromatography revealed that adrenal microsomes converted BP to primarily a phenolic metabolite with a retention time identical to that of 3-hydroxy-BP. Liver microsomes, by contrast, produced approx equal amounts of compounds co-chromatographing with 3-hydroxy-BP and BP-4,5-dihydrodiol. Small amounts of other metabolites were also produced by adrenal and hepatic microsomes. Liver microsomes catalyzed the conversion of BP to metabolites that became covalently bound to exogenous DNA. The amount of binding was dependent upon the duration of incubation and concentration of microsomal protein. Adrenal microsomes, by contrast, did not promote BP binding to DNA. Inhibition of microsomal epoxide hydratase activity with trichloropropene oxide (TCPO) blocked the formation of dihydrodiol metabolites of BP by adrenal and liver microsomes. In the presence of TCPO, liver microsomes produced large amounts of a BP metabolite co-chromatographing with BP-4,5-oxide. TCPO also increased the rate of production of DNA-binding metabolites by liver microsomes but had no effect on the formation of DNA-binding metabolites by adrenal microsomes. The results demonstrated major differences in the pathways of BP metabolism by guinea pig adrenal and hepatic microsomes. Although adrenal microsomes metabolize BP more rapidly than hepatic microsomes, far greater amounts of reactive metabolites are produced by the liver. Thus, adrenal metabolism of BP may be of little toxicological significance. (Author abstract) (48 Refs)

4. BENZO(A)PYRENE PHENOL PRODUCTION BY PERFUSED RAT LIVER AND ITS INHIBITION BY ETHANOL.

Reinke LA, McManus P, Kauffman FC, Thurman RG
Dept. Pharmacology, Univ. Oklahoma Health Sciences Center, Oklahoma City, OK, 73190
Cancer Res; 42(5):1681-1685 1982

A rapid and inexpensive method has been developed to estimate rates of benzo(a)pyrene phenol production by perfused rat liver. This method is based on the measurement of benzo(a)pyrene phenols utilizing a simple fluorometric procedure. Within 2 to 3 min after infusion of benzo(a)pyrene bound to serum albumin, phenols are excreted into the perfusate, primarily as glucuronide and sulfate conjugates. Maximal rates of phenol release were 8 to 10 nmol/g/hr in livers from control rats and 40 to 42 nmol/g/hr in livers from 3-methylcholanthrene-treated rats. Fasting of 3-methylcholanthrene treated rats for 24 hr prior to perfusion experiments did not affect either the rate of phenol production or the extent of their conjugation. Ethanol (20 mM) inhibited rates of phenol formation by 50% in livers from fasted, 3-methylcholanthrene-treated rats but had no effect on benzo(a)pyrene hydroxylase activity in isolated hepatic microsomes. These data indicate that ethanol inhibits phenol formation from benzo(a)pyrene in intact liver, probably by diminishing the supply of the cofactor reduced nicotinamide adenine dinucleotide phosphate. (Author abstract) (22 Refs)

5. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS AND COVALENT BINDING OF METABOLITES TO PROTEIN IN RAT ADRENAL GLAND.

Montelius J, Pasadopoulos D, Bergsson M, Rydstrom J
(c/o Rydstrom) Dept. Biochemistry, Arrhenius Lab., Univ. Stockholm, S-106 91 Stockholm, Sweden
Cancer Res; 42(4):1479-1486 1982

The metabolism of the carcinogenic and adrenocorticolytic polycyclic aromatic hydrocarbon 7,12-dimethylbenz(a)anthracene in rat adrenals was investigated. Both 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene, which also is a well-known carcinogen but has no short-term effects on rat adrenals, appear to be metabolized by one common type of cytochrome P-450-dependent monooxygenase localized in the endoplasmic reticulum. Studies of the kinetic properties of this cytochrome P-450 reveal that the Km values for 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene are lower than 3 uM. Identification of metabolites indicates that, with both 7,12-dimethylbenz(a)anthracene and benzo(a)pyrene, phenols and diols were formed the relative rates of formation of which were markedly influenced by the epoxides hydrase inhibitor cyclohexane oxide, suggesting that epoxides are intermediate metabolites. Added or endogenous microsomal glutathione S-transferase B had little or no effect on the distribution of metabolites. A rather selective binding of metabolites of 7,12-dimethylbenz(a)anthracene to soluble and microsomal proteins was demonstrated. The adrenal cytochrome P-450 involved in the conversion of these polycyclic aromatic hydrocarbons appears to be unrelated to those responsible for the synthesis of mineralocorticoids and glucocorticoids from cholesterol. Among androgens and estrogens, estradiol proved to be the most inhibitory steroid, suggesting a role of the hydrocarbon-metabolizing cytochrome P-450 in estrogen biosynthesis. However, no such function could be demonstrated conclusively. The metabolite patterns and the effects of nonsteroid inhibitors of liver monooxygenases, eg, alpha-naphthoflavone, SU 9055, and ellipticine, suggest that the properties of this cytochrome P-450 resemble those of the 3-methyl-cholanthrene-inducible cytochrome P-488 from rat liver. (Author abstract) (38 Refs)

6. SELECTIVE ACTIVATION OF SOME DIHYDRODIOLS OF SEVERAL POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENIC PRODUCTS BY PROSTAGLANDIN SYNTHETASE.

Guthrie I, Robertson IG, Zeiger E, Boyd JA, Eling TE
(c/o Eling) Lab. Pulmonary Function and Toxicology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Cancer Res; 42(5):1620-1623 1982

The ability of prostaglandin synthetase (PGS) to cooxidize benzo(a)pyrene, benzo(a)anthracene, chrysene, and several of their dihydrodiol derivatives to mutagenic products was tested with Salmonella typhimurium strain TA98 and TA100. The microsomal fraction of ram seminal vesicles, a known source of PGS, in the presence of the PGS substrate arachidonic acid, metabolized benzo(a)pyrene-7,8-dihydrodiol, benzo(a)anthracene-3,4-dihydrodiol, and chrysene-1,2-dihydrodiol to mutagenic products. This activity was inhibited by the PGS inhibitor indomethacin. Unlike the PGS system, however, a cytochrome P-450-reduced nicotinamide adenine dinucleotide phosphate-dependent system present in an Aroclor 1254-induced rat liver 9,000 x g supernatant fraction, also activated the parent compounds [benzo(a)pyrene, benzo(a)anthracene, chrysene] and several other benzo(a)anthracene dihydrodiols (the 1,2-dihydrodiol, the 8,9-dihydrodiol, and the 10,11-dihydrodiol). The chrysene trans-3,4, trans-5,6, and cis-5,6 diols were not activated to mutagens by either system. Thus, the PGS system appears to be more selective than does the cytochrome P-450 system in the activation of polycyclic aromatic hydrocarbons to mutagenic products, activating only those dihydrodiols with adjacent double bonds in the bay region from which the bay-region diol-epoxides are formed. (Author abstract) (20 Refs)

7. INACTIVATION OF A DIOL EPOXIDE BY DIHYDRODIOL DEHYDROGENASE BUT NOT BY TWO EPOXIDE HYDROLASES.

Glatt HR, Cooper CS, Grover PL, Sims P, Bentley P, Merdes M, Waechter F, Vogel K, Guenthner TM, Oesch F
Inst. Pharmacology, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Science; 215(4539):1507-1509 1982

The mutagenicity of r-8,t-9-dihydroxy-3-10,11-oxy 8,9,10,11 tetrahydrobenz[a]anthracene (BA-8,9-diol 10,11-oxide) toward Salmonella typhimurium TA 100 is not decreased by the presence of large amounts of highly purified microsomal or cytosolic epoxide hydrolase. However, highly purified dihydrodiol dehydrogenase inactivates this diol epoxide, which is a major DNA-binding metabolite of benz[a]anthracene. The K-region epoxide, benz[a]anthracene 5,6-oxide (BA 5,6-oxide) is efficiently inactivated by microsomal epoxide hydrolase, is much less readily inactivated by cytosolic epoxide hydrolase, and is not inactivated by dihydrodiol dehydrogenase. This inactivation of a diol epoxide by dihydrodiol dehydrogenase points to a new significance of this enzyme and a new level of control for diol epoxides. (Author abstract) (32 Refs)

8. METABOLISM OF BENZO(A)PYRENE IN EPIDERMAL KERATINOCYTES AND DERMAL FIBROBLASTS OF HUMANS AND MICE WITH REFERENCE TO VARIATION AMONG SPECIES, INDIVIDUALS, AND CELL TYPES.

Kuroki T, Hosoni J, Munakata K, Onizuka T, Terauchi M, Nemoto N
Dept. Pathobiochemical Cell Res., Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan
Cancer Res; 42(5):1859-1865 1982

The metabolism of benzo(a)pyrene (BP) in epidermal keratinocytes and dermal fibroblasts of humans and mice was investigated with emphasis on variation among species, individuals, and cell types. Human epidermal and dermal cells were isolated from the skin of normal subjects following separation of the epidermis from the dermis with forceps. Metabolic activity of human epidermal cells on BP was consistently demonstrated by cell-mediated assay. Mutation of the V79 cells, measured as ouabain resistance, was induced in a dose-related fashion, although the extent of induced mutation varied from 5 to 22 ouabain-resistant colonies per 10(5) survivors/10 uM BP in cultures derived from different individuals. The most striking observation was that human dermal fibroblasts did not activate BP to a form that was mutagenic to cocultured V79 cells. This was observed without exception in all nine cultures of dermal fibroblasts and the one culture of embryo fibroblasts (IMR-90) tested. Analysis by high-pressure liquid chromatography indicated that human epidermal and dermal cells both metabolized BP, producing almost the whole series of known metabolites of BP. The amount of BP 7,8-dihydrodiol, a proximate metabolite of BP, produced by human dermal cells varied from 0.2 to 2.7% of the total BP added and seemed to be enough to induce

mutation. Furthermore, human dermal cells not necessarily activated exogenously added BP 7,8-dihydrodiol to a form being mutagenic to V79 cells. These observations suggest that further metabolism of BP 7,8-dihydrodiol is partially or entirely blocked in human fibroblasts. In contrast to human fibroblasts, mouse fibroblasts isolated from the dermis of embryos did activate BP and induced mutation in cocultured V79 cells to a higher extent than did mouse epidermal cells, indicating interspecies variation in metabolic activation of BP between human and mouse fibroblasts. (26 Refs)

BINDING TO CELLULAR MACROMOLECULES

9. EXCISION OF BENZO[A]PYRENE DIOL EPOXIDE I ADDUCTS FROM NUCLEOSOMAL DNA OF CONFLUENT NORMAL HUMAN FIBROBLASTS.

Kaneko M, Cerutti PA
(c/o Cerutti) Dept. Carcinogenesis, Swiss Inst. Experimental Cancer Res., CH-1066 Epalinges s/Lausanne, Switzerland
Chem Biol Interact; 38(3):261-274 1982

The formation and removal of covalent adducts of racemic 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE I) was studied in nucleosomal DNA of confluent cultures of normal human fibroblasts (NF). For this purpose NF were prelabeled in their DNA with [14C]-thymidine and treated with [3H]BPDE I. The adducts were composed of 77% (7R)-N2-(7beta,8alpha,9alpha-trihydroxy-7,8,9,10 tetrahydrobenzo[a]pyrene-10 yl)deoxyguanosine, 12% of the corresponding 7S-enantiomer and of minor amounts of adducts to cytosine and adenine. The adduct composition did not change significantly in 24-hr post treatment incubation. Bulk mononucleosomes were prepared from micrococcal nuclease digested nuclei and their DNA analyzed by gel electrophoresis. The adduct concentrations were determined in 145 base pair (bp) nucleosomal core-DNA, 165 bp chromatosomal DNA and in total nuclear DNA. From these data the concentration in nucleosomal linker-DNA was calculated. The initial adduct distribution was non-random and 6.3 times higher in 47 bp linker-DNA relative to 145 bp core-DNA and 9.2 times higher in 27 bp linker-DNA relative to 165 bp chromatosomal DNA. Adduct removal was very rapid during the first 8 hr and more efficient from linker-DNA than from core DNA. After this early phase the adducts located in 145 bp core-DNA became refractory to further excision and represent a major fraction of the adducts persisting in DNA of NF over a prolonged period. In contrast, further adduct removal was observed from nucleosomal linker-DNA. (Author abstract) (31 Refs)

10. BENZPYRENE GROUPS BIND PREFERENTIALLY TO THE DNA OF ACTIVE CHROMATIN IN HUMAN LUNG CELLS.

Arrand JE, Murray AW
Dept. Biochemistry, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Nucleic Acids Res; 10(5):1547-1555 1982

The cells of the bronchial epithelium of man are targets for benzo(a)pyrene carcinogenesis. When cultures of these cells, and of non-target fibroblasts, are exposed to [3H]benzo(a)pyrene, we find that the epithelial cells metabolize and bind to DNA far greater amounts of benzpyrene than do fibroblasts. By analysis of nuclei of benzyprene-treated cells for sensitivity to limited digestion with pancreatic DNase I, we have shown that benzpyrene groups bind initially to the DNA of expressed (DNase I sensitive) regions of chromatin in both cell types. Covalent binding of benzpyrene groups to nonexpressed (DNase I resistant) regions follows rapidly in the target epithelial cells. These maintain high levels of carcinogen adducts in their DNA. In fibroblasts, benzyprene group binding to non expressed DNA occurs more slowly and active removal of adducts from the DNA is evident. (Author abstract) (21 Refs)

11. ASSOCIATIONS OF BENZO[A]PYRENE WITH RAT-LIVER CHROMATIN AND THE CHROMATIN PROTEIN.

Kaneko M, Hikino Y, Sugano K
(c/o Sugano) Faculty Pharmaceutical Sciences, Toyama Medical and Pharmaceutical Univ., Sugitani, Toyama 930-01, Japan
Chem Biol Interact; 39(1):17-30 1982

Rat-liver nuclei were prepared in the course of time after the ip injection of [G-3H] benzo[a]pyrene ([3H]BP). The nuclei were lysed in the hypotonic buffer and centrifuged at 4000 x g. The recovery of the radioactivity of resulting supernatant (chromatin) was thus 91% at 24 hr, 68% at 48 hr and 74% at 168 hr after the ip injection. The incorporation into nucleosome-oligomer fraction was always much more than into those of monomer and DNA-rich fractions. The preferential incorporation was found in the fraction which was enriched in nonhistone chromatin proteins (NHCPs) of 49,000-55,000 daltons. This fraction steadily raised the incorporation level until at 168 hr after the ip injection. In contrast, the levels of histone and DNA fractions were always very low. The significant incorporation was observed in the fraction which was composed of five classes of histones and low mol wt NHCPs (less than 30,000 daltons), despite the very low incorporation into the histone fraction. The fluorographic analysis revealed the predominant incorporations at the positions of mol wt of 65,000, 52,000 and 44,000 daltons. In addition, the incorporations were clearly observed at the positions of 59,000, 49,000, 45,000, H1 histone, A24 protein and another one. On the other hand, these fractions were, at the final preparation steps, subjected to either dialysis or SDS-phenol treatment and/or acetone precipitation. The total recovery of radioactivity was thus 21% at 24 hr, 32% at 48 hr, and 52% at 168 hr after the ip injection. These results suggest that the chromatin contains considerable amounts of water-soluble, phenol and/or acetone-soluble BP-conjugates in the early period after the ip injection. (Author abstract) (37 Refs)

MORPHOLOGICAL AND BIOCHEMICAL

EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

12. DIFFERENT EFFECTS OF DIMETHYLBENZ(A)ANTHRACENE AND TETRADECANOYLPHORBOL ACETATE ON DIFFERENTIATION OF MAST CELLS IN THE SKIN OF MICE.

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Am J Pathol; 106(3):312-317 1982

The effects of the application of 7,12-dimethylbenz(a)anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA) on the differentiation of tissue mast cells were investigated. Giant granules of beige (C57BL/6-bgJ/bgJ, Chediak-Higashi syndrome) mice were used to distinguish different populations of mast cells. In the normal C57BL/6 mice that had been irradiated and injected with bone marrow cells of beige C57BL/6 mice (bgJ/bgJ to +/+ chimeras), mast cells in the skin remained normal in type and mast-cell precursors in the bone marrow and peripheral blood were of the beige type. When DMBA was painted onto the skin of such bgJ/bgJ to +/+ chimeras, the number of beige mast cells increased, but the number of normal mast cells did not change. On the other hand, the number of both normal and beige mast cells increased when TPA was applied to the bgJ/bgJ to +/+ chimeras. Autoradiographic study showed that beige mast cells proliferated more than normal mast cells after DMBA applications, whereas the proliferation was comparable in both types of mast cells after TPA applications. The present results indicate that the effects of DMBA applications on differentiation of mast cells are different from those of TPA applications. (Author abstract) (18 Refs)

13. DETECTION OF DUCTAL DYSPLASIA IN MAMMARY OUTGROWTHS DERIVED FROM CARCINOGEN-TREATED VIRGIN FEMALE BALB/C MICE.

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Cancer Res; 42(5):1753-1760 1982

These studies were undertaken to determine if altered growth potential of mammary epithelial cells could be detected in outgrowths derived from monodispersed mammary cells of virgin female BALB/c mice previously exposed to ionizing radiation or 7,12-dimethylbenz(a)anthracene (DMBA). Monodispersed mammary epithelial cells were obtained by enzymatic dissociation of mammary tissues of 12 wk-old virgin female BALB/c mice. Twenty-four hr prior to cell dissociation, donor animals were exposed to either 100 rads of gamma-ray irradiation, 0.25 mg of DMBA, or 0.075 mg of DMBA. Control donors were untreated. Mammary outgrowths were derived by injecting cells into the gland-free mammary fat pads of 3-wk-old virgin female BALB/c mice. Ten wk after the injection, the outgrowths were examined and classified. The data indicated that treatment of donor animals with either gamma-radiation or DMBA increased the frequency of ductal lesions over control levels. Both the frequency and severity of the lesions depended on the number of cells which were injected. When outgrowths were derived by injection of 10(5) cells into the gland-free fat pads, only a few severe lesions were detected. In outgrowths derived from 10(4) cells, less severe lesions (Class I lesions) were common in all groups and occurred in approximately 10 to 15% of the outgrowths. The frequency of severe (Class II and III) ductal dysplasia, however, was increased by treatment in these groups, occurring in 4.5% of control outgrowths in 15.6, 14.9, and 14.3% of the outgrowths derived from donor cells treated with 100 rads gamma-rays, 0.075 mg DMBA, and 0.25 mg DMBA, respectively. Thus, these data indicated that ductal dysplasias were more common and more severe in outgrowths derived from 10(4) rather than 10(5) cells. The ductal lesions observed in this study resembled both morphologically and histologically ductal abnormalities which have been associated with the pathogenesis of mammary carcinoma in both rats and mice. (29 Refs)

14. CYTOCHEMICAL MARKERS OF BLADDER CARCINOGENESIS.

Wilson PD, Summerhayes IC, Hodges GM, Trejdosiewicz LK, Nathrath WJ
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Histochem J; 13(6):989-1007 1981

Enzyme cytochemical and immunocytochemical techniques were used at the light and electron microscope levels to study the distribution of potential enzyme and antigen markers of chemical transformation in rat and mouse bladders. In in vivo methylnitrosourea-induced rat tumors, alkaline phosphatase (AP) localization was normal on the external surface of the plasma membranes of some cells whereas in others AP was detected only on intracellular membranes. 5'-Nucleotidase (5NU) localization was abnormal in all cells, being seen on endoplasmic reticulum and nuclear membranes only, while in normal bladders only ectoenzyme localization was seen. After tumors were cultured as explants for 15 days, heterogeneity of AP and 5NU localization was seen on the plasma membranes. Enzyme production within some cells was variable while in other cells, only parts of the membrane reacted heavily. A bimodal pattern of AP localization was seen in transformed cell cultures and tumors of mouse bladder derived by in vitro treatment of explants with dimethylbenz(a)anthracene. Cells had either normal ectoenzyme reaction product or abnormal intracellular membrane reaction product. 5NU and adenosine diphosphatase were lost and an Mg.ATPase and a cyclic AMP-independent, calcium-insensitive 'protein phosphatase' were induced in transformed cell cultures. Immunocytochemical study revealed an epithelial antigen in the cytoplasm of both normal and transformed cells which was associated with reticular cytoplasmic ground substance, plasma membrane vesicles and cytoskeletal elements. (29 Refs)

15. THE EFFECT OF BENZO(A)PYRENE ON DNA SYNTHESIS AND DNA POLYMERASE ACTIVITY OF RAT LIVER MITOCHONDRIA.

Salazar I, Tarrago-Litvak L, Gil L, Litvak S
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FEBS Lett; 138(1):45-49 1982

DNA synthesis in liver mitochondria of benzo(a)pyrene (BP; 40 mg/kg)-treated rats was higher than in mitochondria from untreated rats, both at different protein concentrations and over different incubation times, but the solubilized mitochondrial DNA polymerase activity was higher in the control preparation. Dideoxythymidine triphosphate (ddTTP) inhibited DNA synthesis in whole mitochondrial preparations, with a much more profound effect in mitochondria from untreated rats. Detergent treatment showed that the difference between treated and untreated mitochondria was not due to BP effect

on organelle membrane permeability. Ethidium bromide produced a polymerase inhibiting effect similar to that of ddTTP, but aphidicolin did not. (21 Refs)

16. INDUCTION OF NEONATAL RAT SKIN AND LIVER ARYL HYDROCARBON HYDROXYLASE BY COAL TAR AND ITS CONSTITUENTS.

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J Invest Dermatol; 78(3):227-229 1982

Topical application of coal tar solution (USP) to neonatal rats resulted in the induction of skin and liver aryl hydrocarbon hydroxylase (AHH) activities. Furthermore indirect exposure of the animals to coal tar vapors resulted in induction of the enzyme in skin and liver. Cutaneous application of coal tar to pregnant rats resulted in induction of skin and liver AHH activity in both mothers and prenatal rats. Among several defined constituents of coal tar tested benzo(a)pyrene (BP), anthracene and acridine were found to have measurable induction effects on neonatal rat skin and liver AHH. These studies indicate that therapeutic coal tar solution as well as selected defined chemical constituents of coal tar are capable of altering the activity of AHH in skin and liver. (Author abstract) (25 Refs)

17. MEMBRANE-BOUND SIALOGLYCOPROTEINS FROM RAT LIVER AFTER COMBINED EXPOSURE TO BENZO(A)PYRENE AND SULFUR DIOXIDE.

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Vopr Med Khim; 27(6):791-794 1981

The effect of carcinogens on metabolism of membrane-bound sialoglycoproteins (MBSGP) was studied in random-bred albino male rats. Animals were exposed to benzo(a)pyrene (BP) in combination with sulfur dioxide (SD). Within 2 wk, 6 wk, and 6 mo after exposure, rats were sacrificed and the distribution of MBSGP in the liver was determined. Combined exposure to BP and SD resulted in the increase of N-acetylneuraminic acid content in liver mitochondria and liver lysosomes, decrease of neuraminidase activity, and increase of betagalactosidase activity. Carcinogens did not affect lipid peroxidation in the liver tissue. (20 Refs) (In RUS)

18. DNA METHYLATION LEVELS IN NORMAL AND CHEMICALLY-TRANSFORMED MOUSE 3T3 CELLS.

Diala ES, Hoffman RM
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Biochem Biophys Res Commun; 104(4):1489-1494 1982

Normal mouse embryo 3T3 cells grown in culture and cells transformed by benzo(a)pyrene and methylcholanthrene were analyzed by high performance liquid chromatography (HPLC) to determine the 5-methylcytosine to cytosine base ratios in their total genomic DNA. The DNA methylation levels were approx equal in the three cell lines. Findings obtained with HPLC and those obtained by other techniques are discussed. (15 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

19. EFFECTS OF NORETHYNODREL ON NEOPLASMS IN THE BUCCAL POUCH OF THE SYRIAN HAMSTER.

Frensilli JA, Weatherred JG
416 Hungerford Dr., Rockville, MD, 20850
Oral Surg; 53(3):288-292 1982

This study was instituted to determine the effect of a progestin, norethynodrel, on the induction of experimental carcinomas of the hamster cheek pouch. Thirty-six Syrian hamsters were divided into two groups. One group received 2 mg/kg/day of norethynodrel in sc injections, and the other group received nothing. The right cheek pouches of both groups were painted 3x a wk with the chemical carcinogen 9,10-dimethyl-1,2-benzanthracene in a 0.05% acetone solution. After 9 wk of painting, the first tumors developed in the hormone-treated hamsters, while none appeared in the control group until after 10 wk. After 15 wk, 100% of both groups had tumors. The average latent period was 11.8 wk for the treated group and 12.7 wk for the control group, (p = less than 0.05%, Student's test). Norethynodrel significantly decreased the induction time of the neoplasms. (Author abstract) (12 Refs)

20. 2-BROMO-ALPHA-ERGOCRYPTINE (CB-154) AND TAMOXIFEN (ICI 46,474) INDUCED SUPPRESSION OF THE GENESIS OF MAMMARY CARCINOMAS IN FEMALE RATS TREATED WITH 7,12-DIMETHYLBENZANTHRACENE (DMBA): A COMPARISON.

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Oncology; 39(2):88-92 1982

Daily treatment of female Sprague-Dawley rats with 2-bromo-alpha-ergocryptine (CB-154) (prolactin suppressor) or Tamoxifen (estrogen antagonist) for 33 days before and after 7,12-dimethylbenzanthracene (DMBA) administration reduced (p less than 0.05) the incidence of mammary carcinomas by 58 and 49%, respectively. A combination of CB-154 and Tamoxifen further reduced (p less than 0.05) mammary carcinoma incidence by an additional 50-59%. Treatment with Tamoxifen for 66 days beginning 33 days after carcinogen treatment reduced (p less than 0.05) the incidence of mammary carcinomas by 65%; CB-154 treatment, during the same time period, did not significantly effect the final yield of mammary carcinomas. The combination of Tamoxifen and CB-154 was comparable to Tamoxifen alone in suppressing the incidence of mammary carcinomas in the latter study. These results demonstrate a substantial suppressive and synergistic effect of Tamoxifen and CB-154 in the initiating phases of mammary carcinogenesis while in the early promoting phases of this oncogenic process, short-term treatment with Tamoxifen was superior to CB-154 treatment; no synergism between these clinically important compounds was observed. (Author abstract) (27 Refs)

21. EFFECTS OF ESTROGENS ON ARYL HYDROCARBON HYDROXYLASE MEDIATED BINDING OF BENZO(A)PYRENE METABOLITES TO DNA IN VITRO.

Williams MT, Hendley R
Dept. Biochemistry, Coll. Medicine, Univ. South Florida, Tampa, FL, 33612
Biochem Biophys Res Commun; 104(4):1349-1355 1982

Liver microsomes from mice injected with 0.1 or 2 mg of estradiol (ES) 24 hr prior to, during and 24 hr after injection of 3-methylcholanthrene (MC), exhibited a significantly decreased capacity to mediate the binding of benzo(a)pyrene metabolites to DNA, compared to microsomes from mice which received only MC. The enzyme and cytochrome components of the aryl hydrocarbon hydroxylase (AHH) were not affected by either ES treatment, suggesting ES may act as a non-competitive inhibitor of AHH activity. (20 Refs)

22. EFFECT OF RETINYL ACETATE ON THE OCCURRENCE OF OVARIAN HORMONE-RESPONSIVE AND -NONRESPONSIVE MAMMARY CANCERS IN THE RAT.

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Dept. Home Economics, Univ. New Hampshire, Pettee Hall, Durham, NH, 03824
Cancer Res; 42(3):903-905 1982

The inhibitory activity of retinyl acetate against the induction of ovarian hormone-responsive and -nonresponsive mammary gland adenocarcinomas was studied in intact and castrated female Sprague-Dawley rats. Three experiments were conducted. Mammary cancer was induced by a single po administration of 7,12-dimethylbenz(a)anthracene (DMBA) at 50 days of age. Animals in Experiments 1 and 2 each received 20 mg DMBA, whereas those in Experiment 3 received 15 mg. In all experiments, animals were fed a chow diet supplemented per kg with either a placebo or 328 mg retinyl acetate starting 7 days after carcinogen treatment. In Experiment 1, rats were castrated at either 7, 60, or 90 days postcarcinogen and were killed 120 days after DMBA was given. In Experiment 2, rats were castrated 30 days after DMBA and were killed 240 days after carcinogen treatment. In Experiment 3, rats were castrated when a detected tumor attained a measurable diameter, and the hormone responsiveness of their tumors was subsequently determined. The experiment was terminated 279 days after DMBA treatment. In both intact and castrated rats, mammary tumor occurrence was inhibited by treatment with retinyl acetate. However, there were no differences in the latency to appearance time of hormone-responsive and -nonresponsive cancers in intact animals receiving either placebo or retinyl acetate. The data indicate that retinyl acetate inhibits DMBA-induced mammary tumorigenesis in either the presence or the absence of the ovaries. It appears that retinyl acetate is effective in inhibiting both ovarian hormone-responsive and -nonresponsive mammary tumors. (Author abstract) (15 Refs)

23. EFFECT OF VITAMIN B2 ON TUMORIGENESIS OF 3-METHYLCHOLANTHRENE IN THE MOUSE SKIN.

Ohkoshi M, Ohta H, Ito M
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Gan; 73(1):105-107 1982

Local administration of riboflavin 2',3',4',5'-tetrabutyrate (B2-But4) suppressed the induction of skin tumors in mice by 3-methylcholanthrene. The latent period for the appearance of tumors was markedly delayed in the group treated with B2-But4. These findings suggest that riboflavin might retard the process of skin tumorigenesis. (Author abstract) (11 Refs)

24. INTERACTION OF DIETARY FAT AND THE THYMUS IN THE INDUCTION OF MAMMARY TUMORS BY 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Wagner DA, Naylor PH, Kim U, Shea W, Ip C, Ip MM
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Cancer Res; 42(4):1266-1273 1982

The interaction of dietary fat and the thymus in the induction of mammary tumors by dimethylbenz(a)anthracene has been examined in female Sprague-Dawley rats. In these experiments, rats fed diets of 0.5% (low fat), 5% (normal fat), or 20% (high fat) corn oil from weaning (21 days of age) were thymectomized or sham thymectomized at 35 days of age and were given 5 mg of dimethylbenz(a)anthracene at 55 days of age. Thymectomy exerted a protective effect in rats fed low and normal fat diets, and this was not reversed by Thymosin Fraction V. In high fat-fed rats, tumorigenesis was increased compared to the low fat groups, and in addition, the protective effect of thymectomy was absent. This differential effect of thymectomy could not be explained on the basis of changes in prolactin concentration, since prolactin levels were decreased in all dietary groups. Neither diet nor thymectomy affected corticosterone levels or the estrus cycle of mature rats. Peripheral blood lymphocytes were, however, decreased by both thymectomy and increasing the fat content of the diet. It is hypothesized that the promoting effect of dietary fat on dimethylbenz(a)anthracene-induced mammary tumorigenesis is mediated via the immune system, although a role for the endocrine system still cannot be ruled out. (Author abstract) (66 Refs)

25. THE EFFECTS OF DIETARY SELENIUM ON THE BIOTRANSFORMATION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Schillaci M, Martin SE, Milner JA
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Mutat Res; 101(1):31-37 1982

Effects of dietary selenium on mutagenicity of 7,12-dimethylbenz[a]anthracene (DMBA) following incubation with liver microsomes from Sprague-Dawley rats given Se in drinking water (5 ppm) or in the diet (0.1, 2.5, or 5 ug/g) for 3 wk were investigated. All rats also received 0, 20, 50, 100 or 500 mg Aroclor 1254/kg body wt. Addition of Se to the drinking water significantly reduced final body wt of the rats and increased plasma Se. S9 liver microsome preparations from the rats did not differ in Se content. The number of revertants in the Salmonella typhimurium test increased approx 280% when the amount of Aroclor was increased from 20 to 100 mg/kg. Livers from rats induced with Aroclor (20-100 mg/kg) receiving Se had a reduced ability of S9 preparations to induce transformation of DMBA (71 and 31% reductions in the number of revertants compared with controls at the 20- and 100-mg/kg induction levels, respectively). Se supplementation of the diet significantly reduced the capability of the rat-liver fractions to transform DMBA. With 2.5 ppm Se, the number of revertants/plate decreased from 65 to 37 at the 20-mg/kg level of Aroclor induction. At 50 and 100 mg/kg induction levels, colonies/plate decreased from 159 to 18 and 136 to 41, respectively. Se at 5 ppm reduced the number of revertants/plate from 68 to 20, 154 to 51, and 136 to 47, at the 20-, 50-, and 100-mg/kg

induction levels of Aroclor, respectively. Thus in vivo Se supplementation may reduce susceptibility to various carcinogens. (24 Refs)

26. EFFECT OF BUTYLATED HYDROXYANISOLE, ALPHA-ANGELICA LACTONE, AND BETA-NAPHTHOFLAVONE ON BENZO(A)PYRENE:DNA ADDUCT FORMATION IN VIVO IN THE FORESTOMACH, LUNG, AND LIVER OF MICE.

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Cancer Res; 42(4):1199-1204 1982

The effects of alpha-angelica lactone (alpha-AL), butylated hydroxyanisole (BHA), and beta-naphthoflavone (beta-NF) on the amount of benzo(a)pyrene (BP) metabolite:DNA adducts formed in the forestomach, lung, and liver of ICR/Ha mice were investigated 48 hr after po administration of BP. BP was administered to mice in amounts known to result in BP-induced neoplasia in certain tissues. Analysis of deoxyribonucleosides by high-pressure liquid chromatography showed that several BP metabolite:DNA adducts were formed in each tissue examined. The major identified adduct in each tissue cochromatographed with the (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a)pyrene (BPDEI):deoxyguanosine adduct. The (+-)-7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDEII):deoxyguanosine adduct was detected in each of the tissues. As a percentage of total DNA-associated radioactivity, the BPDEI:DNA and BPDEII:DNA adducts accounted for 14% in the forestomach, 39% in the lung, and 3% in the liver. Another adduct, possibly derived from BP: phenol(s), was detected in lung and liver. Early eluting unidentified DNA-associated radioactivity was also present in each of the tissues and accounted for the majority of the radioactivity (88% in forestomach, 57% in lung, and 97% in liver). Although total DNA-associated radioactivity in liver was approximately 15-fold higher than in lung and 5-fold higher than in forestomach, the specific activities of the BPDEI:adducts and of the BPDEI:adducts were approximately the same in these organs. Addition of alpha-AL or BHA to the diet inhibited BPDEI:DNA adduct formation in the forestomach and liver but not in the lung. The effect of beta-NF was not tissue specific; this aryl hydrocarbon hydroxylase inducer decreased markedly (80 to 90%) BPDEI:DNA adduct formation in all three tissues. The radioactivity associated with the early eluting peaks was also reduced when alpha-AL, BHA, or beta-NF was fed to the mice. The inhibition of BPDEI:DNA and BPDEII:DNA adduct formation by alpha-AL, BHA, and beta-NF is discussed in relation to similar studies where these compounds inhibited BP-induced neoplasia. (Author abstract) (53 Refs)

27. EFFECT OF THE ACTIVE TUMOR PROMOTER, 12-O-TETRADECANOYLPHORBOL-13-ACETATE ON HAIR FOLLICULAR GROWTH AND DEVELOPMENT OF HAIR ANLAGE TUMORS IN THE MOUSE SKIN: A COMPARISON WITH HUMAN ADNEXAL LESIONS.

Bhisey RA, Iyengar B, Sirsat SM
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J Cancer Res Clin Oncol; 102(3):245-252 1982

Effect of the active tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), on the induction of hair follicular growth and possible neoplasia was studied histologically in normal and precancerous mouse skin. Biweekly application of TPA resulted in nevoid proliferation of hair follicles, decreased the latent period of tumor induction, and increased the number of carcinomas of hair follicular origin in mice pretreated with MCA. The experimental tumor induction data was compared with human adnexal tumors of hair follicular origin. Similar types of animal and human lesions could be attributed to the promoter effect alone or to the dual influence of a carcinogen and promoter. (Author abstract) (11 Refs)

28. INTERACTIONS BETWEEN 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) AND REPEATED LOW-LEVEL X RADIATION IN HAMSTER CHEEK POUCH CARCINOGENESIS: DEPENDENCE ON THE RELATIVE TIMING OF DMBA AND RADIATION TREATMENTS.

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Radiat Res; 90(1):155-164 1982

The effects of x-radiation prior to and during treatment with 7,12-dimethylbenz(a)anthracene (DMBA) on enhancement of hamster cheek pouch carcinogenesis were studied. The results were compared with those of previous studies when irradiation was administered during and after DMBA treatment. Young adult male outbred Syrian golden hamsters were assigned to one of four treatment groups: x-radiation alone (R: 20 R to head and neck per wk for 17 wk); DMBA alone (C: 0.1% in 0.05 ml mineral oil 2x/wk for 11 wk omitting wk 6); x-radiation plus mineral oil (R + MO); and x-radiation plus DMBA (R + C). DMBA or MO were applied topically 24 hr prior to and after R; treatment began during wk 10 of irradiation and continued 3 wk beyond the end of irradiation. All animals were sacrificed 37 wk after DMBA treatments began (46 wk after the start of irradiation). No histological changes were detectable with R alone. In one study, preirradiation may have reduced the carcinogenic effect of DMBA, while in the second study, no significant differences between the R + C group and the C group were detected. Thus, repeated exposure to low-level head and neck irradiation prior to and during DMBA treatment had little or no effect on incidence, latent period, or size of tumors induced by DMBA treatment alone. The relative timing of DMBA and x-ray treatments may be important in determining whether such treatment will interact and produce more tumors than DMBA alone; a period of x-ray/chemical treatment overlap may be necessary for enhancement. (36 Refs)

29. EFFECTS OF HYDROXYUREA AND BENZO(A)PYRENE ON DNA SYNTHESIS IN THE ISOLATED PERFUSED RAT LUNG.

Imamura T, Raby WF, Goldman ME, Wogan GN, Brunengraber H
Dept. Entomology, Univ. California, Riverside, CA, 92521
Bull Environ Contam Toxicol; 28(2):135-140 1982

An isolated perfused rat lung model was used to determine DNA synthesis in the lung tissue, response of DNA synthesis to hydroxyurea (HU), and effect of in vivo pretreatment with benzo(a)pyrene (BP) on DNA synthesis in the rat lung. DNA synthesis was determined in perfused rat lung by incorporation of (3H)thymidine into lung DNA isolated by neutral density gradient centrifugation. An av of 0.75 mg DNA was obtained from approx 750 mg of lung tissue. (3H)Thymidine incorporation was reduced by over 95% by treatment with 10 milliM HU. Lactate/pyruvate ratios were within the normal physiological range at all HU concentrations tested. Perfusion of rat

lungs with 5-50 milliM HU rapidly inhibited lung DNA synthesis with values ranging from 94-97%. With the use of lungs from rats that had been pretreated with BP (6 mg/kg in corn oil, ip for 3 days), DNA synthesis was inhibited by 60%, although there was no indication of lung damage. DNA synthesis was inhibited by 90-95% with HU both in lungs from BP-treated rats and lungs from corn oil only controls; there was no significant difference between the two groups. (11 Refs)

30. EFFECTS OF POLYCHLORINATED BIPHENYLS AND ENVIRONMENTAL TEMPERATURE ON IN VITRO FORMATION OF BENZO[A]PYRENE METABOLITES BY LIVER OF TROUT (SALMO GAIRDNERI).

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Biochem Pharmacol; 31(4):561-566 1982

Rainbow trout (Salmo gairdneri) held at 7 C and 16 C were given Aroclor 1254 (PCB) (10 mg/kg body wt) via ip injections. The binding of [3H] benzo[a]pyrene (BaP) to deproteinized salmon sperm DNA was assayed (pmoles BaP equivalents per mg DNA per mg protein) using the post-mitochondrial supernatant (S 10) fractions from livers of fish at 24-168 hr after the PCB exposure. Liver enzymes from the untreated fish acclimated at 7 C yielded an av binding value (0.37 +-0.17) which was significantly greater (p less than 0.05) than the value (0.07 +-0.03) for untreated fish at 16 C. Liver supernatant fractions from PCB-induced fish acclimated at 16 C and sampled at 24-120 hr showed a substantial increase (p less than 0.05) in the binding (av value 2.4 +-1.8) compared to the value obtained with untreated fish at 16 C. At 24, 48 and 120 hr after the PCB treatment of fish held at 7 C, there was no significant increase in the binding value or extent of metabolism of BaP compared to that obtained with the untreated fish at 7 C. However, at 168 hr, three of four fish at 7 C responded to the PCB treatment with significantly (p less than 0.05) increased binding values (3.5 +-1.6). Chromatographic analyses of the ethyl acetate-soluble metabolites revealed that 3-hydroxy BaP and 7,8-and 9,10-dihydrodiols were the major metabolites; K-region metabolites were formed in trace amounts in untreated and PCB-treated fish at both temperatures. No marked qualitative differences were observed in metabolite profiles after the PCB treatment; however, overall metabolism of BaP and production of reactive metabolites by liver enzymes were considerably (p less than 0.05) enhanced in the PCB-induced fish at both 7 C and 16 C. (Author abstract) (42 Refs)

31. INDUCTION OF GAMMAGLUTAMYLTRANSPEPTIDASE-POSITIVE ALTERED HEPATOCYTIC LESIONS BY COMBINATION OF TRANSPLACENTAL-INITIATION AND POSTNATAL-SELECTION.

Ogawa K, Yokokawa K, Tomoyori T, Onoe T
Dept. Pathology, Sapporo Medical Coll., Sapporo 060, Japan
Int J Cancer; 29(3):333-336 1982

The purpose of this study was to induce in postnatal life the selective growth of altered hepatocytic populations which had been induced in utero by various chemicals. Pregnant rats of a Wistar strain were given a single dose of various chemical carcinogens on the 18th gestational day. From 2 mo postpartum, both the mothers and offspring were given a diet containing 2-acetylaminofluorene (2-AAF) at a concentration of 0.02% for 2 wk. Then, at the end of the 1st wk after the 2-AAF feeding, a two-thirds partial hepatectomy was performed. All the animals were killed 1 wk after the partial hepatectomy and were examined for the incidence of gamma-glutamyltranspeptidase (GGT)-positive altered hepatocytic foci in the liver. The transplacental administration of not only a hepatic carcinogen, diethylnitrosamine (DEN) but also 7,12-dimethylbenzanthracene (DMBA), which does not usually produce hepatocellular carcinomas in adult rats, induced GGT-positive altered hepatocytes in the liver of the offspring. These hepatocytes grew into grossly visible hyperplastic nodules within a wk after the two-thirds partial hepatectomy. The possible applicability of the transplacental initiation-postnatal selection model for the short-term assay of transplacental carcinogenicity is discussed. (Author abstract) (21 Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

32. INDUCTION OF SQUAMOUS CELL CARCINOMA WITH 3,4-BENZO[A]PYRENE IN THE HUMAN BRONCHUS TRANSPLANTED INTO NUDE MICE.

Ito M, Tamada J, Aoki M
Dept. Thoracic Surgery, Chest Disease Res. Inst., Kyoto Univ., Shogoin Kawaharamachi, Sakyo-ku, Kyoto 606, Japan
Gan; 73(1):141-146 1982

By the intraluminal injection of 3,4-benzo[a]pyrene into human bronchial grafts in nude mice, squamous cell carcinoma was induced in 1 bronchial graft out of 17 benzo[a]pyrene-treated grafts. As benzo[a]pyrene is one of the most common carcinogens in the human environment, this experimental system should serve as an excellent model system for studying the process of carcinogenesis in the human respiratory tract. (Author abstract) (7 Refs)

33. SQUAMOUS CELL CARCINOMA ARISING FROM AN EPIDERMOID CYST IN THE OVARY OF A RAT TREATED WITH 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Nishida T, Oda T, Sugiyama T, Nishida T, Nishimura H, Tsunawaki A, Yakushiji M
Dept. Obstetrics and Gynecology, Kurume Univ. Sch. Medicine, 67, Asahi-machi, Kurume-shi, Fukuoka-ken 830, Japan
Gan; 73(1):153-157 1982

Primary non-teratomatous ovarian squamous cell carcinomas are very rare. A case of rat ovarian squamous cell carcinoma has been found in which the tumor arose from a squamous element in the ovary. Squamous epithelial aggregates were found in the wall of a cyst and on serial section, the cyst was found to be unaccompanied by any teratomatous components and showed a thin squamous epithelial lining with keratinizing debris. On the basis of these findings, it was suggested that the squamous element was a rat ovarian epidermoid cyst from which a squamous cell carcinoma arose, presumably by a direct carcinogenic effect of 7,12-dimethylbenz[a]anthracene. (Author abstract) (13 Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

34. TEST-CONDITION-DEPENDENT INFLUENCE OF HARMAN AND NORHARMAN ON BENZO[A]PYRENE MUTAGENESIS IN SALMONELLA.

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Institut fur allgemeine Botanik, Abteilung Mikrobiologie, Universitat Hamburg, Jungiusstrasse 6, 2000 Hamburg 36, W. Germany
Mutat Res; 104(1-3):9-15 1982

The influence of harman and norharman on benzo[a]pyrene [BaP] mutagenicity was examined under various experimental conditions in the Ames test to elucidate contradictory reports of mutagenic, co-mutagenic, and non mutagenic activities of the compounds. Conditions varied were the nature and amount of metabolizing system (S9) preparation, amount of co-factors, and relative proportion of test chemicals. Harman and norharman were not mutagenic using this test system. Activation by 3-methylcholanthrene-, phenobarbital-, and Aroclor 1254-induced mouse liver homogenates led to decreased mutagenicity of BaP in Salmonella typhimurium TA98 upon addition of harman or norharman. Under conditions of activation by Aroclor 1254 induced rat liver homogenate, harman increased BaP revertants while norharman did not affect BaP mutagenicity. Using phenobarbital-induced mouse liver homogenate, varying the S9 extract amount, the amount of cofactors, or the relative proportions of test substances, within certain limits, had no effect on harman or norharman antagonism of BaP mutagenesis. While the Ames test is valuable in qualitatively determining mutagenicity/non-mutagenicity of single chemicals different S9 extracts can yield widely varying results when assessing the possible synergistic or antagonistic effects of further chemicals. (8 Refs)

35. THE EFFECT OF LIVER POSTMITOCHONDRIAL FRACTION CONCENTRATION FROM AROCLOR 1254-TREATED RATS ON PROMUTAGEN ACTIVATION IN L5178Y CELLS.

Amacher DE, Turner GN
Dept. Safety Evaluation Dept., Pfizer Central Res., Groton, CN, 06340
Mutat Res; 97(2):131-137 1982

Mouse L5178Y/TK+/- cells (strain 3.7.2C) were exposed to N-acetyl-2-aminofluorene (AAF: 50 or 67 ug/ml), 2-aminoanthracene (AA: 0.96 ug/ml), benzanthracene (BA: 7.35 ug/ml), benzo(a)pyrene (BP: 2.5 ug/ml), dimethylnitrosamine (DMN: 74.1 ug/ml), or 3-methylcholanthrene (MCA: 5.4 ug/ml), in the presence of varying concentrations (0.5-10%, vol/vol) of liver S9 postmitochondrial fraction from Aroclor-treated male CD rats. With AAF, AA, BA, BP, and MCA, the occurrence of trifluorothymidine-resistant mutants (TFTr) declined in proportion to increases in the S9 concentration during the 3-hr incubation period. With DMN, the occurrence of TFTr mutants increased moderately in proportion to increases in the S9 concentration during the 3-hr incubation period. The results suggest that two different metabolic events may be involved: activation via non-induced factors (perhaps enzymes) whose activities are totally dependent on the vol of S9 (DMN), and deactivation via induced detoxification pathways in a sequence favored by increasing the S9 concentration (the other promutagens tested). The use of a 'standard' concentration (10%) of rat liver S9 did not seem to provide optimal metabolic activation for any of the promutagens except DMN. With the other promutagens, the greatest degree of activation was observed at the lowest S9 concentration studied. (11 Refs)

36. INFLUENCE OF LIVER S-9 PREPARATIONS FROM RATS AND RAINBOW TROUT ON THE ACTIVITY OF FOUR MUTAGENS.

De Flora S, Zanacchi P, Benicelli C, Arillo A
Inst. Hygiene, Sch. Medicine, Univ. Genoa, 16132 Genoa, Italy
Toxicol Lett; 10(4):345-349 1982

The effects of rat and trout liver post-mitochondrial fractions on benzo(a)pyrene (BP), 2-aminofluorene (2-AF), aflatoxin B1 (AFB1), and sodium dichromate in the Ames reversion assay were compared. Rat preparations were significantly more efficient in activating AFB1 and 2-AF. Rat and trout preparations were equally effective in decreasing the direct mutagenicity of sodium dichromate. Rat microsomes were virtually ineffective and trout preparations were slightly active in producing mutagenic metabolites from BP. (14 Refs)

37. INDUCTION OF CYTOTOXICITY, MUTATION, CYTOGENETIC CHANGES, AND NEOPLASTIC TRANSFORMATION BY BENZO(A)PYRENE AND DERIVATIVES IN C3H/10T1/2 CLONE 8 MOUSE FIBROBLASTS.

Gehly EB, Landolph JR, Heidelberger C, Nagasawa H, Little JB
(c/o Heidelberger) Cancer Res. Lab., Univ. Southern California Comprehensive Cancer Center, Los Angeles, CA, 90033
Cancer Res; 42(5):1866-1875 1982

Benzo(a)pyrene (BaP), a series of its metabolic derivatives, and benzo(e)pyrene, a very weakly carcinogenic isomer, were tested for their biological effects on transformable C3H/10T1/2 cells. These cells were used as targets in a series of assays designed to measure oncogenic transformation, mutation to ouabain resistance, cytotoxicity, and induction of cytogenetic changes, as evidenced by chromosomal aberrations and sister chromatid exchange. Of all the compounds tested, only the parent hydrocarbon, BaP, and (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene were found to be significantly active in producing transformation and cytogenetic alterations. BaP, (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene, and (+-)-7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene however were all effective inducers of mutation in C3H/10T1/2 cells. (+-)-7alpha,8beta-Dihydroxy-9beta,10beta-epoxy-7,8,9, 10-tetrahydrobenzo(a)pyrene was the most potent agent in tests for cytotoxicity Benzo(e)pyrene was inactive in all assays examined. Among the compounds tested, there was a correlation between the ability to induce cytogenetic changes and the ability to produce mutation and transformation. These results support the demonstrated role of (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene as a proximal carcinogenic form of BaP and illustrate the utility of the C3H/10T1/2 cell system as an important tool for the detection of genotoxic damage by carcinogenic chemicals. (Author abstract) (47 Refs)

38. INDUCTION OF 6-THIOGUANINE-RESISTANT MUTATIONS BY RAT-LIVER HOMOGENATE (S9)-ACTIVATED PROMUTAGENS IN HUMAN EMBRYONIC SKIN FIBROBLASTS.

Chen DJ, Okinaka RT, Straiste GF, Barnhart BJ
Genetic Group, LS-3, MS896, Los Alamos Natl. Lab., Los Alamos, NM, 87545
Mutat Res; 101(1):87-98 1982

A quantitative mutation assay consisting of early passage of cultured human fibroblasts together with an exogenous rat-liver microsomal preparation to activate promutagens capable

of inducing cytotoxic and mutagenic responses is described. Optimal conditions for a 6-thioguanine (6-TG) resistance mutation assay in the diploid human embryonic skin fibroblast strain (GM10), were investigated. The promutagens used were benzo[a]pyrene (BaP), 3-methylcholanthrene (3MC), and dimethylnitrosamine (DMN). At a constant amount of S9 protein concentration, a linear correlation between mutagenicity and dose was observed. At 50% survival, the mutation frequencies of BaP and 3MC (5 ug/ml) were 60 and 30x the background frequency, respectively, and DMN (5 mg/ml) induced 6-TG mutant frequencies 25x more than background. 3MC and BaP (5 ug/ml) decreased the colony-forming ability of GM10 to 50 and 20%, respectively, DMN at concentrations of 1 and 5 mg/ml inhibited colony-forming ability between 21 and 60%. At high S9 concentrations, a deactivation or detoxification phenomenon was observed. When the mutagenic efficiency of S9-activated chemicals was plotted as the number of induced mutations vs log survival it was not affected by the deactivation capacity of S9 proteins. (42 Refs)

39. THE USE OF PRIMARY RAT HEPATOCYTES IN ACHIEVE METABOLIC ACTIVATION OF PROMUTAGENS IN THE CHINESE HAMSTER OVARY/ HYPOXANTHINE-GUANINE PHOSPHORIBOSYL TRANSFERASE MUTATIONAL ASSAY.

Bermudez E, Couch DB, Tillery D
(c/o Couch), Chemical Industry Inst. Toxicology, P. O. Box 12137, Research Triangle Park, NC, 27709
Environ Mutagen; 4(6):675-68 1982

Details are presented of a method used to evaluate the use of primary rat hepatocyte-mediated mutagenicity with the use of the Chinese hamster ovary (CHO)/hypoxanthine-guanine phosphoribosyl transferase mutational assay. Aflatoxin B1 (AFB1), 7,12-dimethylbenz(a)anthracene (DMBA), and benzo(a)pyrene produced increases in mutant fractions of treated CHO cells as a function of concentration. The time required for optimum expression of mutant phenotype was approx 8 days after exposure to DMBA and AFB1. (35 Refs)

40. CELL-MEDIATED MUTAGENICITY IN CHINESE HAMSTER V79 CELLS OF DIBENZOPYRENES AND THEIR BAY-REGION FLUORINE-SUBSTITUTED DERIVATIVES.

Hass BS, McKeown CK, Sardella DJ, Boger E, Ghoshal PK, Huberman E
Toxicology Dept., Shell Development Co., Westhollow Res. Center, Box 822, Houston, TX, 77001
Cancer Res; 42(5):1646-1649 1982

The polycyclic aromatic hydrocarbons dibenzo(a,i)pyrene and dibenzo(a,h)pyrene, each of which possesses two bay regions, and their bay-region difluorinated derivatives were tested for mutagenicity for ouabain and 6-thioguanine resistance in Chinese hamster V79 cells. Since V79 cells do not metabolize polycyclic aromatic hydrocarbons, mutagenesis was tested in both the presence and the absence of golden hamster embryo cells capable of metabolizing polycyclic aromatic hydrocarbons. Neither of the dibenzopyrenes nor their fluorinated derivatives were mutagenic in the absence of the golden hamster embryo cells. In the presence of these cells (cell-mediated assay), both dibenzopyrenes were mutagenic whereas the difluorinated derivatives, 2,10-difluorodibenzo(a,i)pyrene and 3,10-difluorodibenzo(a,h)pyrene, either were inactive or exhibited (on a dose basis) a weak response. However, the mutagenicity of the dibenzopyrenes was eliminated when they were coincubated with 7,8-benzoflavone, a mixed-function oxidase inhibitor. The results suggest that metabolic oxidation of these polycyclic aromatic hydrocarbons at the bay region (presumably to diol-epoxides) is required for a mutagenic response in the cell-mediated assay. (Author abstract) (35 Refs)

41. QUANTITATIVE CORRELATIONS AMONGST ALKALINE DNA FRAGMENTATION, DNA COVALENT BINDING, MUTAGENICITY IN THE AMES TEST AND CARCINOGENICITY, FOR 21 COMPOUNDS.

Parodi S, Taningher M, Boero F, Santi L
Istituto Scientifico per lo Studio e la Cura dei Tumori, Viale Benedetto XV, 10 I-16132 Genova, Italy
Mutat Res; 95(1):1-24 1982

Correlations between the carcinogenicity of 21 compounds and the alkaline DNA fragmentation, formation of DNA adducts, and Ames-test mutagenicity produced by the compounds were studied. Test compounds included 6 methylating agents, 3 ethylating agents, 5 aromatic amines, 2 polycyclic aromatic hydrocarbons, and 5 heterogeneous compounds thought to generate DNA adducts with greater steric hindrance than those produced by methylating or ethylating agents. Compounds were administered to adult mice and rats by oral and parenteral routes. The highest doses exceeded lethal levels. Parameters measured included the oncogenic potency index (OPI), covalent binding index (CBI), DNA fragmentation index (DFI), mutagenic potency index (MPI), and lethal dose index (LDI). All parameters were found to be correlated with carcinogenic potency, the correlation between CBI in vivo and carcinogenicity was 3x as great as the correlation between the MPI and carcinogenicity. CBI in vivo correlated strongly with DFI in vivo. Assay of the DFI for eight compounds indicated negative results for benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, 2-acetylaminofluorene, and urethane; positive results were obtained for methyl methanesulfonate, aniline, 2-naphthylamine, and benzidine. Results indicate that carcinogenic potential should be predictable from the results of a battery of appropriate tests. (75 Refs)

42. RELATIONSHIP BETWEEN FLUORESCENCE OF POLYNUCLEAR AROMATIC HYDROCARBONS IN COMPLEX ENVIRONMENTAL MIXTURES AND SAMPLE MUTAGENICITY.

Litten S, Babsh JG, Pastel M, Werner MB, Johnson B
Toxic Substances Control Unit, Div. Water, New York State Dept. Environmental Conservation, Albany, NY, 12233
Bull Environ Contam Toxicol; 28(2):141-148 1982

The relationship between polynuclear aromatic hydrocarbon fluorescence on thin layer chromatography plates and mutagenicity assays was studied in extracts of 92 samples from sites in New York State. Samples included sewage plant sludges, industrially and non-industrially affected soils and sediments, material from landfills, and biological samples from a variety of urban and rural settings. About 30 g (4 g for biological samples) were extracted with a mixture of dichloromethane and acetone (4:1). Mutagenicity assays were performed with Salmonella typhimurium strains TA98 and TA100. A positive response was defined as a two-fold or greater increase in revertants, ie, a mutagenic index (MI) of 2 or more. Compounds with an MI less than 2 were considered nonmutagenic. Overall, 89% of the 92 samples exhibited fluorescence, and 51% mutagenicity. There was generally a good correlation between fluorescence and mutagenicity in the different types of samples, both being highest in industrially affected samples. The eight biological samples exhibited no fluorescence and two were mu-

tagenic. Significant associations were found between fluorescence and mutagenicity for TA98 with and without activation and for TA100 with activation. A study of the overall association of fluorescence and mutagenicity in the various tests indicates that samples demonstrating fluorescence were over 5x as likely to be mutagenic than nonfluorescent samples. (15 Refs)

43. PLASMA ALPHA-FETOPROTEIN ELEVATION AND MUTAGENICITY OF URINE AS EARLY PREDICTORS OF CARCINOGENICITY IN BENZO(A)PYRENE FED RATS.

Boyd JN, Misslbeck N, Babish JG, Campbell TC, Stoewsand GS
Dept. Food Science and Technology, Cornell Univ., New York State Agricultural Experiment Station, Geneva, NY, 14456
Drug Chem Toxicol; 4(3):197-205 1981

Weanling male Fischer rats were fed on diets containing benzo(a)pyrene (BaP) at (a) 0 or 1,000 ppm or (b) 0, 1, or 100 ppm for 11 wk on diet (a) or 8 wk on diet (b). Some of the animals' diet contained 500 ppm sodium phenobarbital (PB) for the last 5 wk (none getting 1,000 ppm BaP). Cardiac blood was obtained weekly at wk three and assayed for alpha-fetoprotein (AFP). Hepatic slices were obtained at wk six and stained for gamma-glutamyl transpeptidase (GGT) activity. Also at wk six 8-hr urine samples were taken and assayed by the Salmonella/mammalian microsomal test with S typhimurium strain T98. The AFP level was independent of all diets except for notable elevation at wk six in the 1,000 ppm BaP animals. Except for 1,000 ppm BaP animals assay for GGT was independent of other variables. The mutagenesis assay was positive only for the 1,000 ppm BaP animals at wk six with and without activation, and for the 100 ppm BaP with PB animals at wk eight with activation. The AFP and urinary mutagenesis assays were recommended as co-tests for short term carcinogenicity potential evaluation. (12 Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

44. ELECTRICALLY INDUCED FLUORESCENCE AS A METHOD FOR STUDYING BENZO[A]PYRENE BINDING TO DNA.

Bader PJ, Jennings BR
Electro-Optic Group, Physics Dept., Brunel Univ., Uxbridge, Middlesex UB8 3PH, England
FEBS Lett; 139(1):101-104 1982

A new physical method developed for studying the binding geometry of fluorescent groups to macromolecules was applied in the study of trans-7,8-dihydroxy-anti-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene derivatives (BPDE), native benzo[a]pyrene (BP), and proflavine, when independently bound to DNA. The method is sensitive to the presence of small amounts of bound dye molecules on nucleic acid. Results indicate that the pyrene fluorophore of BPDE does not intercalate the DNA helix, at least in the way that proflavine or BP do. The method appears to be an effective indicator of binding geometry for polycyclic hydrocarbons on nucleic acids. (18 Refs)

45. METHODS FOR THE RECOVERY OF ORGANIC CARCINOGENS FROM WATER.

Ehrlich K, Cawley G, Klein R
Gulf South Res. Inst., New Orleans, LA
Sci Tech Aerosp Rep; 19(24):3372 1981

The organic carcinogens benzo(a)pyrene, dieldrin, and N-acetyl-2-aminofluorene were recovered on XAD-2 macroreticular resin in yields of 90% or more from distilled water or seawater or in yields of 40% or more from Lake Pontchartrain water containing a high concentration of organic material. The original solutions contained less than 500 parts per trillion of carcinogen. These results show that XAD-2 provides an efficient means for recovering nonpolar organic carcinogens from dilute solutions. (Author abstract) (no Refs)

REVIEWS AND OTHER RELATED STUDIES

46. STUDIES ON THE MECHANISMS INVOLVED IN MULTISTAGE CARCINOGENESIS IN MOUSE SKIN.

Slaga TJ, Fischer SM, Weeks CE, Klein-Szanto AJ, Reiners J
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
J Cell Biochem; 18(1):99-115 1982

Skin tumors can be induced in mice by repeated applications of a carcinogen (complete carcinogenesis) or one subthreshold dose of a carcinogen followed by repeated applications of a weak or noncarcinogenic tumor promoter (initiation-promotion carcinogenesis). Of several mouse strains studied, Sencar was the most sensitive to both types of carcinogenesis. An important aspect of tumor initiation by polycyclic aromatic hydrocarbons (PAH) is their metabolism to an electrophilic intermediate(s) which interacts covalently with epidermal DNA. Tumor promotion can be divided into at least two stages: the first obtainable by limited treatment with 12-O-tetradecaroylphorbol-13-acetate (TPA) or certain nonpromoters; the second obtainable by repeated applications of mezerein. The dark basal keratinocytes (primitive stem cells) are important in the first stage of promotion. Most of the other cellular and biochemical events associated with promotion are actually associated with the second stage. Some evidence has been found suggesting that strain and/or stock differences in responses to complete and/or multistep carcinogenesis represent differences in responses to complete and/or promotion. Although C57BL/6 mice are relatively resistant to PAH initiation and phorbol ester promotion, they are fairly sensitive to complete carcinogenesis by PAH, suggesting that this strain is resistant to phorbol ester tumor promotion. Sencar and C57BL/6 mice seem to respond qualitatively but not quantitatively to one application of TPA. (97 Refs)

47. MUTAGENS, CARCINOGENS AND THE WATER CYCLE.

Tye RJ, Waite WM, Bell VJ, Forster R, Blackmore D, Klemparer R, Starling D, Nome GP
Finham Regional Lab., Severn-Trent Water Authority, Severn-Trent, England
Water Pollut Control; 80(5):606-613 1981

Systems which are regarded as of potential application to the testing of chemicals in waters with emphasis on those systems used or proposed for use by the Severn-Trent Water Authority Mutagenicity Unit (STMU) are discussed. Currently the most widely used mutagenicity testing systems utilize bacteria as test

organisms. The two species of bacteria most commonly used, Salmonella typhimurium and Escherichia coli, have been modified to increase their sensitivity in assays. Mammalian cell transformation assays using a line of hamster kidney fibroblast cells grown as monolayers on solid surfaces is probably the most promising non-bacterial testing system. Work in the STMU has been restricted to the study of organics, especially haloforms and polycyclic aromatic hydrocarbons, although they are not the only active constituents in water implicated in carcinogenesis. Approx 20% organic chemicals have been identified in water samples. The study shows that mutagenic responses may be induced by a wide range of both raw and treated waters using a tube-fluctuation test without prior concentration. Concentration of trace organics in water is discussed. Results of any bacterial mutagenicity assay show whether the test material can cause a statistically significant increase over the spontaneous rate at which mutations occur. Demonstration of bacterial mutagenesis is not a demonstration of hazard to human health. Mutagenesis testing can be applied either to natural water samples or to materials shown to be present in waters by analytical techniques and subsequently tested as pure substances. (17 Refs)

48. HYGIENIC STANDARDIZATION AND EVALUATION OF CARCINOGENIC SUBSTANCES.

Ianysheva NIa, Chernchenko IA, Balenko NV
A. N. Marzeev Res Inst. General and Community Hygiene, Kiev, USSR
Gig Sanit; (12):4-7 1981

Approaches to the estimation of max permissible doses (MPD) of carcinogenic substances are discussed with special emphasis on the concept of threshold effect of carcinogens. Experiments in CC57BR and CC57BL mice exposed to benzo(a)pyrene (BP) showed the existence of critical doses. Administration of doses exceeding the critical level did not result in a further increase of the incidence of BP-induced tumors. It was suggested that estimation of MPD should include testing of carcinogens in a wide range of doses (from the minimal effective to the max ineffective), follow-up of animals throughout their entire lifespan, mathematical simulation of dose-effect and dose-time relationships, prediction of the risk of tumor development after exposure to small doses of carcinogens, and extrapolation of the MDP estimated in animal experiments to humans. (15 Refs) (In RUS)

49. CONTRIBUTION OF 1-NITROPYRENE TO DIRECT-ACTING AMES ASSAY MUTAGENICITIES OF DIESEL PARTICULATE EXTRACTS.

Salmeen I, Durisin AM, Prater TJ, Riley T, Schuetzle D
Engineering and Res. Staff Ford Motor Co., P.O. Box 2053, Dearborn, MI, 48121
Mutat Res; 104(1-3):17-23 1982

The percentage contribution [P] of 1-nitropyrene [1-NP], a derivative of the carcinogenic polycyclic aromatic hydrocarbons, to the direct-acting Ames Salmonella assay mutagenicities of extracts of exhaust particles collected from three different diesel powered vehicles was assessed. 1-NP was shown to be a substantial contributor to the Ames assay mutagenicities for the three diesel particulate extracts examined. For Salmonella strains TA98, TA100, and TA1538, respectively, P was 16, approx 1, and 7% for one vehicle (1-NP = 2,030 +-220 ppm); 24, 9, and 17% for the second vehicle (1-NP = 150 +-30 ppm); and 13, 4, and 13% for the third vehicle (1-NP = 55 +-11 ppm). Using this assay system, even a 1% contribution of a single compound is important, considering the several hundreds of compounds present in the particulate extracts. Salmonella-histidine reversion assays indicated that the extract matrix had little effect on the mutagenicity of 1-NP. The significance of diesel exhaust-associated 1-NP in relation to adverse effects on human health was discussed. (22 Refs)

50. DIRECT-ACTING MUTAGENS IN DIESEL EXHAUSTS: MAGNITUDE OF THE PROBLEM.

Rosenkranz HS
Center for Environmental Health Sciences, Case Western Reserve Univ., Sch. Medicine, Cleveland, OH, 44106
Mutat Res; 101(1):1-10 1982

Widespread and increased use of diesel engines in the United States will be accompanied by an increase in particulate emissions with potential mutagenic and carcinogenic components. The major class of chemicals associated with the mutagenic effect of diesel emissions (DE) is the nitroarenes, particularly the nitropyrenes. DE mutagenic activity is in the range of 15 revertants/ug dichloromethane extract which can be translated into approx 1.25 x 10(6) revertants/g particulate emitted. 1-Nitropyrene (NP) appears to be the major mutagenic species and accounts for approx 20% of the mutagenic activity in DE; the other 80% of activity may be caused by 1,8-dinitropyrene (DNP). Diesel particulate containing 93 and 1.5 ug of NP and DNP, respectively, may account for the observed mutagenic potencies of DE materials. However, lower estimates for the DNP contribution to the total direct-acting mutagenicity of DE extract have been reported. The United States estimated annual output of NP is 14415 kg, and of DNP is 233 kg. When heavy-duty diesels are considered, such estimates would be increased 2.4-fold to determine the total amount of nitropyrenes released yearly. Nitropyrenes are not only mutagenic, but are carcinogenic in rodents. Development of a postcombustion process to reduce the amounts of nitropyrene particulate in DE is feasible and warrants further study. Periodic, mandatory inspection of diesel-powered vehicles is advocated. (70 Refs)

51. THE MUTAGENIC POTENCY OF 1,8-DINITROPYRENE IN CULTURED MOUSE LYMPHOMA CELLS.

Cole J, Arlett CF, Lowe J, Bridges BA
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England
Mutat Res; 93(1):213-220 1982

The mutagenic potency of 1,8-dinitropyrene (18-DNP) was compared with that of 4-nitroquinoline-1-oxide (4NQO) in cultured mouse lymphoma cells. L5178Y cells were grown in suspension culture and cloned in semisolid medium. 1,8-DNP and 4NQO were dissolved in dimethylsulfoxide (DMSO). DMSO alone had no effect on growth, cloning efficiency, or mutation frequency. Mutagenicity of test compounds was measured as the frequency of induction of resistance to 6-thioguanine (TG), methotrexate (MTX), ouabain (OUA), or 1-beta-D-arabinofuranosyl cytosine (ARA-C). Max mutation frequencies were obtained with 48-96-hr exposures for OUA, ARA-C, and MTX and with 144-192-hr exposures for TG. 1,8-DNP was not toxic at concentrations up to the max 2.5 ug/ml. Both 1,8-DNP and 4NQO produced dose-dependent increases in mutation frequencies in all mutation systems. Mutations evidently occurred by base-pair substitutions. Since previous studies had shown that 1,8-DNP produces frame-shift mutations in Salmonella and Escherichia coli, results suggest that 1,8-DNP produces mutations by different mechanisms in bacteria and mammalian cells. Problems of comparing mutagenicity of test chemicals when

concentrations, treatment times, and toxicity are significantly different are discussed. (20 Refs)

52. THE CHEMICAL ACTIVATION OF NON-MUTAGENIC NITRATED POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENS.

Karplusky GE, McCoy EC, Rosenkranz HS
Center for the Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Mutat Res; 92(1/2):29-37 1982

Ames assays in Salmonella strains TA1535, TA100, TA98, and nitroreductase (NRase)-deficient strains TA100NR and TA98NR were performed with 5-nitroquinoline (5-NQ), 6-nitroquinoline (6-NQ), 8-nitroquinoline (8-NQ), 1,8-dinitronaphthalene (1,8-DNN), 1,5-dinitronaphthalene, 4-nitroquinoline 1-oxide, 2-nitrofluorene, and nitrofurantoin, in the presence or absence of rat liver microsomes (S9 mix). Both 5-NQ and 6-NQ were direct-acting bacteria mutagens, but 8-NQ (a carcinogen in rats) and 1,8-DNN (an analog of 8-NQ) were not mutagenic even in the presence of S9 mix. The non-mutagenicity of 8-NQ and 1,8-DNN could be overcome chemically, in situ, by the addition of zinc (Zn) dust. Anaerobic conditions were not required for a max yield of the mutagenic product of 1,8-DNN. The mutagenicity of the 1,8-DNN product was not due to a nitro function, as shown by the fact that it was fully active even in the NRase-deficient strain TA100NR. It is concluded that although bacteria can reduce some nitrated polycyclic aromatic hydrocarbons (N-PAH) to mutagens, their NRases cannot reduce the nitro functions of all N-PAHs to the proximate mutagenic hydroxylamines. Chemical reduction of the N-PAH (ie, non-enzymatic activation) with Zn (which is compatible with the Ames bioassay) may be a useful addition to the procedure in the evaluation of the potential mutagenicity of nitro-containing chemicals. (24 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:121-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48105
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Sitteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia
Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews-Endocrinology, 311 pp. 1981.

6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Kvenmark SG, Sitteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-229 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW.
Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):10-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Fend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
Chu KC, Milman HA
NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:221-220 1981

10. REVIEWS IN BIOCHEMICAL TOXICOLOGY.
Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

11. ALCOHOL AND CANCER.
MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 1QE, England
Banbury Rep; 7:71-81 1981

14. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.
Reddy BS, Tanneabaum SR, Wontesano R, Correa P, Hamazel W, Wattenberg LW
Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
Iredale N
Institutul de medicina si farmacie, Cluj-Napoca, Romania
Rev Chir [Oncol]; 20(1):1-9 1981
In RUM

16. THE MEANING OF CANCER 'DIETS'.
Jung WF
Abt. f. Onkologie-Hamatologie, Medizinische Klinik C, CH-900: St. Gallen, Switzerland
MMW; 124(2):26-28 1982
In GER

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

17. RISK FACTORS FOR CERVICAL CANCER.
Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

18. EPIDEMIOLOGY OF THE MOST FREQUENTLY OCCURRING TUMORS OF THE DIGESTIVE SYSTEM.
Nauiokas-Heinrich S, Dolle W
Abteilung Innere Medizin I, Universitatsklinik, Ottfried-Muller-Strasse 10, D-7400 Tubingen, W. Germany
Int Arch Allergy Immunol (Berlin); 23(1-1-9 1982
In GER

19. BLADDER CANCER.
Skrabanek P, Walsh A
Epidemiology Unit, Mater Misericordiae Hosp., Dublin, Ireland
UICC Tech Rep Ser 60: 192 pp., 1981.

20. RECENT ADVANCES IN CANCER CYTOGENETICS.
Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2095 1981
In RUS

21. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.
Sasaki M
Chromosome Res. Unit, Hokkaido Univ., Faculty Science, Sapporo 060, Japan
Cancer Genet Cytogenet; 5(2):153-179 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

22. ASBESTOS-RELATED DISEASES.
Casey KR, Rom WN, Moatamed F
Building 512, RMOCEH, Univ. Utah Medical Center, Salt Lake City, UT 84112
Clin Chest Med; 2(2):179-202 1981

23. NONASBESTOS FIBROUS MINERALS.
Lockey JE
Building 512, RMOCEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981.

24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
Lowen GM
Center Natural Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St. Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Vilkas G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-121 1982
In FRE

27. MIGHT CANCER BE A FAILED RESPONSE TO RENEGADE MITOCHONDRIA?
Hartung J
Dept. Anesthesiology, State Univ. New York, Downstate Medical Center, Brooklyn, NY 11203
J Theor Biol; 94(1):173-175 1982

MODIFICATION OF CARCINOGENESIS

28. EFFECT OF GEROPROTECTORS ON CARCINOGENESIS.
Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(3):445-472 1981
In RUS

29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
Hilf R, Sitteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-337 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ONCOGENES.
Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
Univ. Dept. Oral Medicine and Pathology, Immunology Unit, Glasgow Dental Hosp., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
Oral Surg; 53(2):157-169 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.
Troako JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsuhimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI 48824
Gann Monogr Cancer Res; 27:159-179 1982

35. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.
Vainio H, Sorsa M, Rantanen J, Hemminki K, Attio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290, Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

36. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.
Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P2AE, England
J Sci Food Agric; 33(1):39-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Don GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.
Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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CHEMICAL CARCINOGENESIS

Polycyclic Aromatic Hydrocarbons and Related Compounds

SERIES CK07 No. 82/09

SEPTEMBER, 1982

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. LONG-TERM STUDY OF LIVER DAMAGE FOLLOWING SUBCUTANEOUS INJECTION OF AIRBORNE PARTICLE EXTRACTS AND POLYCYCLIC AROMATIC HYDROCARBON FRACTIONS.

Mohr R, Heinrich U, Offermann M, Themann H
Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Nottulner Landweg 102, D-4400 Munster-Roxel, W. Germany
Int Arch Occup Environ Health; 49(3/4):305-314 1982

Female NMRI mice, 9-12 wk old, were given a single sc injection of a suspension of either the total extract of particulates from city air or the total polycyclic aromatic hydrocarbon portion of the extract. Both samples contained 3 ug of benzo(a)pyrene. Fifteen mo later, when most of the mice had developed injection-site tumors, the livers were examined by electron microscopy for alterations in the hepatic parenchyma. There was no histological evidence of metastasis in the livers of either group. (28 Refs)

2. COMPARATIVE TUMOR-INITIATING ACTIVITY OF COMPLEX MIXTURES FROM ENVIRONMENTAL PARTICULATE EMISSIONS ON SENCAR MOUSE SKIN.

Nesnow S, Triplett LL, Slaga TJ
Carcinogenesis and Metabolism Branch (MD-68), United States Environmental Protection Agency, Genetic Toxicology Div., Health Effects Res. Lab., Research Triangle Park, NC, 27711
JNCI, 68(5):829-834 1982

The value of the SENCAR mouse for testing tumorigenic properties of complex mixtures on mouse skin was studied. Seven complex mixtures were obtained as dichloromethane extracts of collected particulate emissions from three diesel-fueled automobiles, a heavy-duty diesel engine, a nonleaded gasoline-fueled automobile, a coke oven battery, and a roofing tar pot. These emissions were applied topically at multiple doses to both male and female SENCAR mice that were subsequently promoted with 12-O-tetradecanoylphorbol 13-acetate. Two statistical analyses were applied to the data to rank the samples and to provide 95% confidence intervals. One analysis used tumor multiplicity data, applied them to a nonlinear Poisson model, and the second analysis used tumor incidence data and applied them to a log-probit model. Both analyses ranked the complex mixtures in similar order. Benzo[a]pyrene content alone could not account for all the tumorigenic activity in each complex mixture, indicating that other components also contribute to the overall tumorigenic activity. (Author abstract) (27 Refs)

3. A COHORT STUDY ON MORTALITY AMONG LONG-TIME EMPLOYED SWEDISH CHIMNEY SWEEPS.

Hogstedt C, Andersson K, Frenning B, Gustavsson A
Dept. Occupational Medicine, Natl. Board Occupational Safety and Health, S-171 84 Solna, Sweden
Scand J Work Environ Health; 8(Suppl1):72-78 1982

A cohort study was performed on all members of the Swedish Chimney Sweeps Union who were active in 1950 or later and who were members for at least 10 yr. A total of 2,071 sweeps were studied; 2,048 were evaluable. Compared to the national av, the mortality of the exposed cohort was significantly increased (230 observed vs 197.6 expected before the age of 80) due to a greater number of deaths from tumors, particularly lung and esophageal cancer, and from nonmalignant diseases of the respiratory system (chronic bronchitis, emphysema, and asthma). The increased overall mortality was higher among those with shorter exposure time, although esophageal cancer and chronic respiratory diseases were more frequent in long-time exposed individuals. The excess mortality was more predominant among men who left the profession before 1965 than among those who were still working that yr or later. Exposure of chimney sweeps could explain the mortality pattern observed in this study, however, cigarette smoking may have been a contributing factor. Exposure to polycyclic aromatic hydrocarbons, nitrogen compounds, arsenic, and asbestos in combination with promotion from exposure to sulfur dioxide probably caused the increased mortality in these men. (21 Refs)

4. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.

Rom WN, Lee JS, Craft BF
Rocky Mountain Center Occupational and Environmental Health, Dept. Internal Medicine, Family and Community Medicine, Univ. Utah Sch. Medicine, Bldg. 512, Salt Lake City, UT, 84112
Am J Indust Med; 2(3):247-260 1981

Health and safety problems associated with the oil shale industry are reviewed. Polycyclic aromatic hydrocarbons, which are often carcinogenic, may represent a hazard during the retorting and, possibly, the refining processes. Scottish, Estonian, and American health experiences are reviewed. Studies in those countries have shown that potential hazards of the oil shale industry include skin and lung cancers. A number of studies in rodents have demonstrated neoplastic and other cytologic changes after administration of crude oil shale or its constituents via intratracheal, inhalation, or topical routes. Hydro-treating crude oil shale dramatically reduces its carcinogenic potency when applied topically. Results of other rodent studies in which oil shale materials were applied topically, installed intratracheally, or used as bedding material are reviewed. Future prospects for monitoring the health of oil shale workers are discussed. (46 Refs)

5. POLYCYCLIC AROMATIC HYDROCARBONS IN THE OCCUPATIONAL ENVIRONMENT: WITH SPECIAL REFERENCE TO BENZO[A]PYRENE MEASUREMENTS IN SWEDISH INDUSTRY.

Lindsted G, Sollenberg J
Chemistry Dept., Natl. Board Occupational Safety and Health, S-171 84 Solna, Sweden
Scand J Work Environ Health; 8(1):1-19 1982

Aspects of occupational exposure to polycyclic aromatic hydrocarbons (PAH) are reviewed, with emphasis on benzo[a]pyrene (BAP). PAH are widely distributed in the environment and are associated with industrial processes including coking and combustion of carbonaceous materials. Concentrations of PAH in the air in industrial areas are generally 2-3 orders of magnitude less than concentrations in the workplace. The primary sources of PAH are coal tar and pitch. Exposure occurs through the lungs and skin. Samples of PAH are collected on glass fiber or silver film filters and extracted with solvents. Total PAH may be determined or individual compounds may be analyzed by chromatographic methods. Review of studies conducted in various countries indicates that very high exposure to BAP [greater than 10 ug/cubic meter (m3)] occurs in gas and coke works, aluminum works, manufacture of carbon electrodes, handling of molten tar or pitch, chimney sweeping, and use of asphalt mixed with tar. High exposure occurs in blast furnaces and steel works. Findings of epidemi-

ologic studies are contradictory, but some studies indicate an increased risk of lung, bladder, and skin cancers with exposure to PAH. The current threshold limit for exposure to BAP is 0.2 mg/m3. (88 Refs)

6. DETERMINATION OF MUTAGENIC POTENTIAL AND ORGANIC CONTAMINANTS OF GREAT LAKES DRINKING WATER.

Williams DT, Nestmann ER, LeBel GL, Benoit FM, Otson R
Bureau Chemical Hazards Environmental Health Directorate, Dept. Natl. Health and Welfare, Ottawa K1A 0L2, Canada
Chemosphere; 11(3):263-276 1982

Summer and winter water samples taken directly from 12 treatment plants were passed through ion exchange resin filters to extract organic contaminants. Water grab samples of raw and treated water were also taken at each plant at the same time and analyzed for volatile organics. The resin extracts were tested for mutagenicity with/without S9 activation against Salmonella typhimurium TA98 and TA100. The extracts were also analyzed for organochlorine and organophosphorus pesticides (OPP), trialkylphosphates and triarylphosphates (TAP), polychlorinated biphenyl (PCB), and polycyclic aromatic hydrocarbons (PAH). Extracts taken to dryness were more mutagenic than those left in solution. Mutagenicity was higher in the summer samples (11/12) than winter samples (7/12). Aggregate PAH was higher (11/12) in winter samples however; naphthalene, biphenyl dibenzyl, fluorene, anthracene or phenanthrene, fluoranthrene, pyrene, stilbene, fluorenone, and anthraquinone were found. The extracts contained (a) alpha-BHC and beta-BHC, both generally higher in winter, (b) no PCB or OPP, (c) TAP: ethyl, n-butyl, 2-chloroethyl, 1,3-dichloropropyl, butoxyethyl, phenyl, and cresyl, in seven instances only in summer samples. The grab samples contained bromodichloromethane, chlorodibromoethane, chloroform, toluene, m-xylene, and o-xylene. No relationships between relative mutagenicity and identified contaminants could be deduced. (19 Refs)

7. COMPARATIVE STUDY OF CONTAMINATION OF PLANT FOOD PRODUCTS BY CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS (PAH) IN THE USSR AND GDR.

Shabad LM, Khesina AIa, Solenova LG, Dikun PP, Kalinina IA, Engst R, Fritz V
All-Union Cancer Res. Inst., Moscow, USSR
Vopr Pitan; (1):56-59 1982

The results of comparative evaluation of the concentrations of benzo(a)pyrene (BP) in the soil and in various agricultural plants in the Soviet Union and in the East Germany are reported. The increase of BP level in the soil from 0.5-1,000 ug/kg to greater than 15,000 ug/kg resulted in the increase of BP concentration from 0.4 ug/kg to 17.0 ug/kg in the wheat grain and from 2.0 ug/kg to 10.0 ug/kg in the sunflower seed. (11 Refs) (In RUS)

8. BENZO(A)PYRENE LEVELS IN SAUSAGE PRODUCTS.

Ruchkovskii BS, Tiktin LA, Pallura AN
Dept. Environmental Carcinogens, R. E. Kavetskii Inst. Problems in Oncology, Kiev, USSR
Vopr Pitan; (1):62-63 1982

Benzo(a)pyrene (BP) levels were studied in various sausage products. The highest BP content (3.7 and 2.3 ug/kg) was detected in smoked sausages. Only traces of BP were detected in sausages treated with smoking liquid 'Vakhtol'. (9 Refs) (In RUS)

9. STUDY OF SOIL BENZO(A)PYRENE UPTAKE BY POTATO TUBERS AND WHEAT AND MILLET GRAINS.

Dikun PP, Kalinina IA, Kaveraz AIa, Zheludeva ZP, Rezchikov VA, Goncharova LM
N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 28(1):54-57 1982

A significant correlation between benz(a)pyrene concentration in soil and potato tubers was established for its soil level of 0.6-20.0 mg/kg. This points to potato uptake of the carcinogen even at low levels of pollution. Absence of correlation between benz(a)pyrene concentrations in grain (husk) and soil even for relatively high levels of soil pollution (up to 320 ug/kg) shows that wheat and millet grains do not absorb the carcinogen. (Author abstract) (15 Refs) (In RUS)

10. COMPARISON OF REGIONAL AND TEMPORAL TRACE SUBSTANCE DISTRIBUTION IN BULK PRECIPITATION AND ATMOSPHERIC DUST.

Thomas W
Lehrstuhl fur Hydrologie, Universitat Bayreuth, Bayreuth, W. Germany
Sci Total Environ; 23:369-378 1982

Regional and temporal variations in polycyclic aromatic hydrocarbons, trace metals, and gamma-benzene hexachloride in bulk precipitation and atmospheric dust were measured for classification of air pollution at 20 stations in Bavaria. Data were analyzed by cluster analysis with Ward's algorithm. Six pollution classes were found. Pollutants showed regional and temporal variations that should be taken into account in studies of air pollution. (16 Refs)

11. PREDICTING POLYCYCLIC AROMATIC HYDROCARBON CONCENTRATIONS IN URBAN AEROSOLS BY LINEAR MULTIPLE REGRESSION ANALYSIS.

Butler JD, Crossley P, Colwill DM
Dept. Chemistry, Univ. Aston, Birmingham B4 7ET, England
Environ Pollut [B]; 3(2):109-123 1982

Polycyclic aromatic hydrocarbons (PAH: pyrene, chrysene, benzo(a)pyrene, benzo(e)pyrene, coronene) in air at a heavy-traffic highway site and a light-traffic suburban site were measured and related to meteorological conditions (windspeed and temperature). PAH were associated with sub-micron particulates; their concentration in air correlated well with meteorological conditions, yielding a better index of the amount of carcinogenic components in the air than the black smoke stain reflectance technique. (16 Refs)

12. EFFECTS OF AMBIENT TEMPERATURE ON ASPECTS OF AIRBORNE POLYCYCLIC AROMATIC HYDROCARBONS.

Yamasaki H, Kuwata K, Miyamoto H
Environmental Pollution Control Center, 62-3, 1 Chome, Nakamichi, Higashinari-ku, Osaka City, 537, Japan
Environ Sci Technol; 16(4):189-194 1982

The presence of various common three- to six-ring polycyclic aromatic hydrocarbon compounds in the air in the vapor and/or particulate state was examined at biweekly intervals over 1 yr. The six-ring compounds o-phenylenepyrene, anthanthrene, and benzo(ghi)perylene were never found in the vapor phase at temperatures up to 29.8 C. Benzofluoroanthene

was not in the vapor phase of 2/28 samples. Benzo(a)pyrene and/or benzo(e)pyrene were not in the vapor phase of 8/28 samples. The other compounds were always in both phases. (33 Refs)

13. APPLICATION OF THE SALMONELLA MUTAGENICITY ASSAY AND DETERMINATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN WORKPLACES EXPOSED TO PETROLEUM PITCH AND PETROLEUM COKE.

Monarca S, Pasquini R, Sforzolini GS, Viola V, Fagioli F
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Int Arch Occup Environ Health; 49(3/4):223-239 1982

The airborne particulates and the petroleum pitch (PP) and petroleum coke (PC) working materials in a carbon electrode factory were assayed for mutagenicity on Salmonella typhimurium TA98 and TA100 with or without S9 activation. The PP contained antanthrene (AA), benzo(k)fluoranthene (BkF), benzo(a)pyrene (BaP), fluoranthene (FA), and perylene (P); the PC contained BkF, BaP, FA, P, and benzo(b)fluoranthene. There was a dose-response mutagenicity relationship (DRMR) between PP extracts and TA98 with S9. The PC extracts were not mutagenic under any condition due to the low levels of the indicated polycyclic aromatic hydrocarbons. Airborne particulates from two distinct sites in the factory contained BkF, BaP, FA, and P, but not in the same ratios; one site also yielded AA. A DRMR was found for extracts from both sites under all conditions except TA100 without S9 at the site lacking AA. The demonstration of mutagenic activity in the airborne particulates not requiring S9 activation indicated the potential adverse effects of the thermal processing of the PP and PC. (41 Refs)

14. THE EFFECT OF BENZO[A]PYRENE ON SPONGES AS MODEL ORGANISMS IN MARINE POLLUTION.

Zahn RK, Kurelec B, Zahn-Daimler G, Muller WE, Rijavec M, Batel P, Given R, Pouljesic V, Beyer R
Physiologisch-Chemisches Institut, Johannes-Gutenberg-Universitat, Duesbergweg, D-6500 Mainz, W. Germany

Chem Biol Interact; 39(2):205-220 1982

The majority of the investigations were performed with the marine sponge Tethya lyncurium at concentrations of 2 x 10(-8) to 1 x 10(-11) g/ml of benzo[a]pyrene (BaP). Sea-pollution was characterized as BaP equivalent activity in the Ames test. Increased activity of ornithine decarboxylase (ODC) was observed when sponges were artificially exposed to polluted marine areas for 3 wk. In contrast, to the situation in higher animals no ODC induction of the fast type was observed. Mixed function oxygenases (MFO) were not detected in sponges nor could they be induced as in vertebrates. BaP was absorbed by Tethya and concentrated 30-60 fold. In live, but not dead, artificially perfused sponges [3H]- and [14C]BaP radiolabel became firmly associated with DNA, RNA and protein of the sponges. The association persisted in isolated fractions, in nucleotides, in nucleosides and in protein hydrolysates. The BaP binding ratio to DNA was found to be strongly correlated to the concentration of BaP. Light modifies BaP and thus enables binding. In the dark only very low association, if any, is observed. The possible consequences of these findings are discussed. (Author abstract) (48 Refs)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

15. A STUDY OF STERIC AND ELECTRONIC FACTORS GOVERNING THE POSITION OF BIOFUNCTIONALIZATION OF THE BENZ(A)ANTHRACENE OF THE BENZ(A)ANTHRACENE NUCLEUS: METABOLISM IN VITRO OR FLUORO- AND METHYL-SUBSTITUTED ANALOGS.

Sheikh YA, Hart RW, Witiak DT
Div. Medicinal Chemistry and Pharmacognosy, Coll. Pharmacy, Comprehensive Cancer Center, Ohio State Univ., Columbus, OH, 43210

Bioorg Chem; 10(4):429-442 1981

The metabolism of benz(a)anthracene (BA) analogs having fluoro groups (positions 3, 5, or 6) and/or methyl groups (positions 7 or 12) and of 7,12-dimethylbenz(a)anthracene analogs having fluoro groups (positions 2, 3, 4, 5, or 6) was studied in rat liver microsome (S-10) fractions induced by phenobarbital, beta-naphthoflavone, or 3-methylcholanthrene. Assays of the metabolites produced from these substrates (notably the dihydrodiol metabolites) suggested that both steric and electronic factors may determine the preferential sites of bioactivation of the BA and DMBA analogs. A hypothesis is presented to account for these findings. (48 Refs)

16. IDENTIFICATION OF METABOLITES OF BENZO[B]FLUORANTHENE.

Amin S, LaVoie EJ, Hecht SS
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Carcinogenesis; 3(2):171-174 1982

The metabolism by rat liver 9,000 x g supernatant of the environmental carcinogen benzo[b]fluoranthene was investigated. The major metabolites were identified, by comparison to synthetic samples, as 5-and 6-hydroxybenzo[b]fluoranthene and 4- or 7-hydroxybenzo[b]fluoranthene. The principal dihydrodiol metabolite formed under these conditions was trans-11,12-dihydro-11,12 dihydroxybenzo[b]fluoranthene, which was identified by comparison to the synthetic compound. 1,2-Dihydro-1,2-dihydroxybenzo[b]fluoranthene was identified, by its mass spectrum and by comparison of its uv spectrum to that of a synthetic model compound, 11-ethylidene-11H-benzo[b]fluorene. No evidence was obtained for the formation of 7b,8-dihydro-7b,8-dihydroxybenzo[b]fluoranthene or trans-9,10-dihydro-9,10-dihydroxybenzo[b]fluoranthene. The latter would be the precursor to a bay region dihydrodiol epoxide of benzo[b]fluoranthene. (Author abstract) (24 Refs)

17. DIFFERENT PATTERNS OF BENZO[A]PYRENE METABOLISM OF PURIFIED CYTOCHROMES P-450 FROM METHYLCHOLANTHRENE, BETA NAPHTHOFLAVONE AND PHENOBARBITAL TREATED RATS.

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Carcinogenesis; 3(2):129-133 1982

An improved high-pressure liquid chromatography system was used to analyze the amount of benzo[a]pyrene metabolites formed in reconstituted microsomal mixed-function oxidase systems containing different cytochromes P-450. We separated

12 identified and 7 unknown metabolites of BP which included 3 diols; the 9,10-, 4,5-, and 7,8-dihydrodiols; 4 phenols, 9-, 7-, 1-, and 3-hydroxybenzo[a]pyrene (OH-BP), and 3 quinones: the 1,6-, 3,6-, and 6,12-quinones. Two additional peaks co-migrated with synthetic 4-OH-BP and 5-OH-BP, respectively. The former, designated fraction 1, was shown by uv spectra to contain primarily the 4,5-epoxide with small amounts of 4-OH-BP. The total metabolism of BP was found to be approx 20-fold greater with the cytochrome P-450 from the 3-methylcholanthrene (P-450 3-MC) and beta-naphthoflavone (P-450 BNF) treated rats than with the phenobarbital reinduced cytochrome P-450 (P-450 PB). 3-OH-BP and 9-OH-BP were the major phenolic products for both P-450 3-MC and P450 BNF whereas the 3OH-BP and 1 OH-BP were the major phenolic products for P-450 PB. The ratio of total phenols to diols was found to be 3.34, 4.85 and 0.70 for P-450 3-MC, P-450 BNF and P-450 PB. The major dihydrodiol generated by P-450 3-MC and P-450 BNF was 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene, whereas the 9,10-diol was the major diol from P-450 PB. The amount of 1,6 and 3,6-quinones produced was greater than the 6,12-quinone with the P-450 3-MC and P-450 BNF but all three quinones were produced in low and equal amounts by the P-450 PB. In respect to the percent metabolites formed at a given region of the BP, P-450 3-MC and P-450 BNF preferred oxidation at the 1, 3 positions, 6 position and the 7, 8 positions, whereas the P-450 PB preferred oxidation at the 4, 5 position. This study demonstrates the unique positional specificity of different forms of cytochrome P-450 which may regulate the balance between activation and detoxification pathways of polycyclic aromatic hydrocarbon metabolism. (Author abstract) (28 Refs)

18. METABOLISM AND DNA BINDING OF BENZO[A]PYRENE IN CULTURED HUMAN BLADDER AND BRONCHUS.

Stoner GD, Daniel FB, Schenck KM, Schut HA, Goldblatt PJ, Sandwisch DW
Dept. Pathology, Medical Coll. Ohio, 3000 Arlington Ave., Toledo, OH, 43614
Carcinogenesis; 3(2):195-201 1982

The metabolism of benzo[a]pyrene (BP) was examined in explant cultures of human bladder and bronchus. Three-day cultures were exposed to radiolabeled BP for 24 hr, and the metabolism was determined by analysis of the level of binding of reactive metabolites to DNA, and by the release of metabolites into the medium. For a given individual, the DNA binding level and extent of metabolism was usually higher in the bladder than in the bronchus. In specimens obtained from 16 individuals, the average DNA-binding levels for BP-DNA adducts following a 24 hr exposure to 1 uM BP were 6.4 +-5.0 umol BP/mol deoxyribonucleotide for the bladder and 3.1 +-1.9 umol BP/mol deoxyribonucleotide for the bronchus. The major BP - DNA adduct in both tissues co-chromatographed with one of the adducts formed by reaction of r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10 tetrahydrobenzo[a]pyrene with deoxyguanosine using high-pressure liquid chromatography. In tissues obtained from the same individual, the binding levels of BP metabolites to bladder cell DNA was not strongly correlated to that of bronchial cell DNA (r = 0.54). The medium of both tissues contained small amounts of free, unconjugated metabolites of BP (less than 3% of the total) and large amounts (30-45% of the total) of unidentified highly polar material. Human bladder appears to be the most active human explant tissue yet studied with respect to its ability to activate BP to DNA binding forms. The relevance of this observation to human bladder cancer is, as yet, unknown. (Author abstract) (40 Refs)

19. THE METABOLISM AND ACTIVATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN EPITHELIAL CELL AGGREGATES AND FIBROBLASTS PREPARED FROM RAT MAMMARY TISSUE.

Cooper CS, Pal K, Hewer A, Grover PL, Sims P
Chester Beatty Res. Inst., Inst. Cancer Res. Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Carcinogenesis; 3(2):203-210 1982

The metabolism of 7,12-dimethylbenz[a]anthracene (DMBA), benzo[a]pyrene (BP) and benz[a]anthracene (BA) by epithelial cell aggregates and fibroblasts in culture has been investigated using mammary tissue obtained from female Wistar rats. The results show that (a) both types of mammary cells metabolize all three hydrocarbons into ether- and water-soluble derivatives; (b) the patterns of metabolites produced by epithelial cells and fibroblasts are similar but that fibroblasts form more of the water-soluble materials; (c) the major dihydrodiols formed are the 8,9-dihydrodiols of BA and DMBA and the 7,8-and 9,10-dihydrodiols of BP; (d) all three hydrocarbons are metabolized to form products that bind covalently to protein but only the potent carcinogens BP and DMBA are metabolized to form derivatives that react covalently with DNA; and (e) the chromatographic profiles of the hydrocarbon-deoxyribonucleoside adducts formed in epithelial cells treated with either BP or DMBA are similar to those obtained in analogous experiments with fibroblasts. (Author abstract) (50 Refs)

20. THE INFLUENCE OF VARIOUS ENZYME INDUCERS ON THE MICROSOMAL METABOLISM OF 7,8-BENZOFLAVONE.

Coombs MM
Chemistry Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Carcinogenesis; 3(2):229-230 1982

Comparative in vitro metabolic experiments with 7,8-benzoflavone using microsomes prepared from the livers of control Sprague-Dawley rats or from rats of the same strain treated with phenobarbitone, 3-methylcholanthrene, or Aroclor 1254 (known inducers of hepatic cytochrome P450) mixed function oxidases) disclosed variable amounts of the three metabolites previously reported, namely the 5,6-epoxide, 9,10-dihydro-9,10-diol, and the 5 (or 6)-phenol. Microsomes from phenobarbitone-treated rats give in addition a small amount of the 5,6-dihydro-5,6-diol, identified by mass spectrometry and uv spectroscopy. The apparent discrepancy between our previous results and those of Nesnow and Bergman is therefore partly resolved, although the absence of the 9,10-diol from their products remains unexplained, but may have resulted from their use of rats of a different strain. (Author abstract) (4 Refs)

21. FUNCTIONAL HETEROGENEITY OF UDP-GLUCURONOSYLTRANSFERASE ACTIVITIES IN C57BL/6 AND DBA/2 MICE.

Bock KW, Lilienblum W, Pfeil H
Dept. Pharmacology and Toxicology, Univ. Gottingen, Kreuzbergring 57, D 3400 Gottingen, W. Germany
Biochem Pharmacol; 31(7):1273-1277 1982

Functional heterogeneity of liver microsomal UDP-glucuronosyltransferase activities towards 1-naphthol, 4-methylumbelliferone or 3-hydroxybenzo(a)pyrene (UDP-GT1 activities) and morphine or 4-hydroxybiphenyl (UDP-GT activities) was studied in two inbred strains of mice which are genetically responsive (C57BL/6) or non-responsive (DBA/2) to methyl-

cholanthrene-induction of drug metabolizing enzymes. 3-Methylcholanthrene preferentially induced UDP-GT1 activities in C57BL/6 mice. Phenobarbital, however, at low doses (50 mg/kg), selectively inhibited UDP-GT2 activities. Higher doses of phenobarbital (80 mg/kg) induced both UDP-GT1 and UDP-GT2 activities. In DBA/2 mice 3-methylcholanthrene-induction of UDP-glucuronosyltransferase activities was not detectable whereas enzyme induction by phenobarbital appeared to be unimpaired. UDP-GT1 activities were ubiquitously detectable in mouse tissues whereas appreciable UDP-GT2 activities were only found in liver and small intestinal mucosa. UDP-GT1 (1-naphthol as substrate) was not inhibited by morphine suggesting different active sites for the conjugation of these substrates. The results suggest the presence of at least two functionally different forms of UDP-glucuronosyltransferase in mice. In conjunction with the results of Owens it is evident that one of these enzyme forms is regulated by the Ah locus (Author abstract) (38 Refs)

22. DISTRIBUTION AND RETENTION OF BENZO(A)PYRENE IN RATS AFTER INHALATION.

Mitchell CE
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. box 589, Albuquerque NM 87185
Toxicol Lett; 11(1/2):35-42 1982

The distribution and retention of inhaled radioactive benzo(a)pyrene (BA) was determined in rats. Twenty-four male Fischer-344 rats were exposed for 1 hr to BAP (500 ug/liter air). Tissue, urine, and fecal radioactivity analyses were performed 2, 3, 6, 12, 24, or 48 hr after exposure. Significant amounts of BAP were found in the stomach, small intestine, trachea, lungs, nasal turbinates, larynx, tracheobronchial lymph nodes, kidneys, and liver immediately after exposure. Fifty per cent of the radioactivity cleared from the respiratory tract within 2-3 hr; the remaining cleared between 25 and 56 hr. Fifty per cent clearance of BAP from the liver was obtained in 6 hr. BAP and metabolite concentration in the kidney reached a max value 6 hr after exposure; subsequent clearance was at a constant rate. Radioactivity levels in the spleen, brain, and testes were lower than other major organs, and remained constant for 24 hr after exposure. Radioactivity accumulated rapidly in the cecum and large intestines and subsequently decreased at a constant rate. Excretion of radioactivity was primarily via the feces. Additional studies are necessary to determine the potential mutagenic or carcinogenic risk of BAP exposure in some tissues. (16 Refs)

23. METABOLISM OF BENZO(A)PYRENE IN RAT BY ORAL ADMINISTRATION.

Yamazaki H, Kumashashi H, Masuda N, Kishi T, Kakiuchi Y, Watabe K, Kondo M
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Chemosphere; 11(5):337-347 1982

Adult male Sprague-Dawley rats were given a single oral dose of tritiated (50 uCi) benzo(a)pyrene (BaP). They were sacrificed at hr 3, 7, 24, and 48. Organs, blood, and urine were assayed for BaP and metabolites. The urinary radioactivity was maximum at hr 7, decreasing slowly thereafter. Blood, kidney, liver, and lung radioactivity levels were at highest at hr 3, dropping sharply by hr 24. At hr 3 the liver contained a relatively high level of benzo(a)pyrene-9,10-diol, with lesser amounts of 3-hydroxybenzo(a)pyrene benzo(a)pyrene-4,5-diol, benzo(a)pyrene-7,8-diol, benzo(a)pyrene-3,6-quinone, benzo(a)pyrene-1,6-quinone, and BaP. At hr 3 the kidney was highest in both quinones, with large amounts of all diols too. Peak amounts occurred in the lung at hr 7, mainly the two quinones and BaP; compared to all other sources the lung contained more metabolites and BaP at hr 48. At hr 7 in the blood the 9,10-diol and BaP were predominant; at hr 7, the 3-hydroxy metabolite prevailed. In contrast to the above sources, the urinary metabolites existed mainly as the glucuronides, mostly as the 3,6-quinone and 9,10-diol at hr 7. (19 Refs)

24. SIMILAR LEVEL OF METABOLIC ACTIVATION OF BENZO(A)PYRENE IN PERFUSED RAT LUNG AND LIVER AND PROTECTION OF LUNG BY LIVER IN A COMBINED PERFUSION SYSTEM.

Klaus E, Foth H, Kahl R, Kahl G
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Biochem Biophys Res Commun; 105(2):596-602 1982

The binding of benzo(a)pyrene metabolites to DNA, RNA, and protein in perfused rat liver and lung in situ and the influence of the liver on the level of nucleic acid and protein modification by benzo(a)pyrene in the lung were investigated. In the liver of 5,6-benzoflavone pretreated rats, irreversible binding of metabolically activated benzo(a)pyrene to both nucleic acids and protein reaches a peak at 15 min and then declines. In contrast, binding in the lung continuously increases over the 2 hr perfusion period. The extent of binding is of the same order of magnitude in the liver and lung of cytochrome P-448-induced (ie 5,6-benzoflavone-induced) animals. At 15 min, binding to both DNA and RNA in the liver exceeds binding to nucleic acids of the lung by a factor of 3-6; this relationship is nearly reversed after 2 hr of perfusion. Protein binding is more pronounced in the lung than in the liver over the entire 2 hr perfusion. The longer persistance of benzo(a)pyrene binding in the lung may contribute to the fact that the lung and not the liver is the target organ of benzo(a)pyrene carcinogenesis. Following the insertion of a liver into the perfusion circuit of the lung, the total irreversible binding of metabolically activated benzo(a)pyrene to DNA, RNA, and protein is reduced, this effect being more pronounced in 5,6-benzoflavone-induced animals. Thus the high detoxication capacity of the liver can protect other organs having lower xenobiotic metabolizing activity against benzo(a)pyrene. (16 Refs)

25. METABOLISM OF 3-HYDROXYBENZO(A)PYRENE IN RAT, ISOLATED HEPATOCYTES AND KIDNEY.

Yamazaki H, Kagita T, Fujiwara M, Kishi T, Kakiuchi Y, Watabe K, Kondo M
(c/o Kaiuchi) Faculty Pharmaceutical Sciences, Kobe Gakuin Univ., 518, Arise, Igawadani, Tarumi, Kobe, 673, Japan
Chemosphere; 11(3):349-353 1982

Adult male Sprague-Dawley rats were given an iv dose of tritiated (0.1 uCi) 3-hydroxybenzo(a)pyrene (3-OHBaP). Urine was collected at hr 24 and 48. The same amount of tritiated 3-OHBaP was also incubated with perfused rat hepatocytes and with sliced rat kidney at 37 C for 2 or 3 hr; extracts were obtained at hr 0.5, 1, 2, and 3 (kidney only). At hr 24 the urine contained benzo(a)pyrene-9,10-diol, benzo(a)pyrene-4,5-diol, benzo(a)pyrene-1,6-quinone, and 3-OHBaP. At hr 48 the urine still contained all of them, but the 9,10-diol was now present only as a glucuronide compared to none at hr 24. All of these metabolites and 3-OHBaP were found in the hepatocytes at all times except for no 1,6-quinone at hr 1, mainly as quinones at all times and 9,10-diol at hr 2. The 3-OHBaP was assayed only as a glucuronide, the 9,10-diol was never found as a glucuronide. In the kidney extracts only quinone metabolites were iden-

tifiable at hr 0.5 and 1. At hr 2 all the diols were present too, mainly 4,5-and 7,8-. At hr 3 not much change had occurred, but the 9,10-diol was present also as a glucuronide; 3-OHBaP was present as a glucuronide (9 Refs)

26. FORMATION OF THE 11,12-DIOL AS A METABOLITE OF BENZO(A)PYRENE BY RAT SKIN IN VIVO.

Weston A, Grover PL, Sims P
Chester Beatty Res. Inst., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England

Biochem Biophys Res Commun; 105(3):935-941 1982

Identification of the 11,12-diol metabolite of benzo(a)pyrene (BP) in rat skin that had been exposed to 3H-BP in vivo is described. High pressure liquid chromatographic analysis revealed that each of the four possible dihydrodiols was formed after application of BP to rat skin. Similar application of BP to mouse skin, however, resulted in the formation of only the 4,5-, 7,8-and 8,10-diols. These findings agree with previous in vitro work. The formation of only two or three dihydrodiols as a result of BP metabolism in a large number of tissues may be indicative of mono-oxygenase specificity. Since four dihydrodiols including the 11,12-diol are formed by oxidation in an ascorbic acid-ferrous sulfate-EDTA system and both K-region double bonds can be attacked by osmium tetroxide. The possibilty exists that BP-11,12-oxide is formed but is removed through conjugation with glutathione, or that BP-11,12-diol is formed but is removed through reaction with glucuronyltransferase or sulfotransferase. However, the 11,12-diol has been identified in vivo. Variations in metabolism and detoxification may be linked with the relative resistance of rat skin to BP carcinogenesis. (27 Refs)

27. THE METABOLISM OF PYRENE BY RAT LIVER MICROSOMES AND THE INFLUENCE OF VARIOUS MONO-OXYGENASE INDUCERS.

Jacob J, Grimmer G, Raab G, Schmoldt A
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Xenobiotica; 12(1):45-53 1982

Pyrene metabolite glc profiles were recorded and metabolites identified by mass spectrometry. Pyrene is metabolized by liver microsomes of untreated rats to 1-hydroxypyrene, 4,5-dihydroxy-4,5-dihydropyrene, two different diphenols and a triol, tentatively identified as 1,4,5-trihydroxy-4,5-dihydropyrene. Pretreatment with phenobarbital or polychlorinated biphenyls favors oxidation at the K-region, whereas cytochrome P-448 inducers stimulate oxidation at the non-K-region of pyrene. 1-Hydroxypyrene does not inhibit pyrene oxidation. Pyrene diphenols are formed by secondary oxidation of 1-hydroxypyrene. Triols are formed from dihydrodiols by secondary oxidation. (Author abstract) (23 Refs)

BINDING TO CELLULAR MACROMOLECULES

28. THE FORMATION OF BENZO[A]PYRENE - DEOXYRIBONUCLEOSIDE ADDUCTS IN VIVO AND IN VITRO.

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Carcinogenesis; 3(3):267-273 1982

The formation of DNA-bound products from benzo[a]pyrene was studied using metabolic activation systems of widely differing cellular and structural integrity. The nature of the benzo[a]pyrene-metaboite-deoxyribonucleoside adducts formed was markedly dependent on the nature of the activation system used. Systems where cellular integrity is preserved, namely mouse skin in vivo and rat liver hepatocytes and lung explants in vitro, when treated with benzo[a]pyrene, formed deoxyribonucleoside adducts of which the major one co-chromatographed with a bay-region diol epoxide-deoxyguanosine adduct 10beta-(deoxyguanosin-N2-yl)-7beta,8alpha,9alpha trihydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene. In striking contrast, the use of activating systems with disrupted cellular integrity such as rat liver, rat lung and mouse skin microsomal fractions in the presence of benzo[a]pyrene and exogenous DNA, resulted in the formation of deoxyribonucleoside adducts derived predominantly from either a further metabolite of 9-hydroxybenzo[a]pyrene or (+-)benzo[a]pyrene-4,5-epoxide. The consequences of such results are important when considering the widespread use of subcellular fractions such as microsomes as metabolic activating systems for short-term mutagenicity and carcinogenicity tests. (Author abstract) (41 Refs)

29. 7,12-DIMETHYLBENZ[A]ANTHRACENE - DEOXYRIBONUCLEOSIDE ADDUCT FORMATION IN VIVO: EVIDENCE FOR THE FORMATION AND BINDING OF A MONOHYDROXYMETHYL-DMBA METABOLITE TO RAT LIVER DNA.

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Carcinogenesis; 3(3):297-301 1982

The polycyclic aromatic hydrocarbon, 7,12-dimethyl benz[a]anthracene (DMBA) is a potent carcinogen to the female Sprague-Dawley rat, and when administered under conditions that have been shown to produce cancer, results in extensive formation of hydrocarbon-deoxyribonucleoside adducts. Sephadex LH-20 and reverse-phase hplc and spectrofluorometric analysis of these adducts demonstrate that at least one adduct results from the binding of 7,12-dimethylbenz[a]anthracene-1,2,3,4-tetrahydro-3,4 dihydroxy-1,2 oxide. In these experiments, employing ip administration of the hydrocarbon, a second more polar adduct was observed. Evidence is presented that this adduct results from the formation of a monohydroxymethyl-methylbenz[a]anthracene-A-ring-diol epoxide. While both of the monohydroxymethyl-DMBA metabolites have been shown to bind cellular DNA following their administration this is the first evidence of monohydroxymethyl-DMBA-deoxyribonucleoside adducts being formed after the administration of DMBA per se. The evidence suggests that this more polar adduct is a 7-hydroxymethyl-12-methylbenz[a]anthracene deoxyribonucleoside adduct. (Author abstract) (35 Refs)

30. MECHANISM FOR THE LOSS OF PREFERENTIAL BENZO[A]PYRENE BINDING TO THE LINKER DNA OF CHROMATIN

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Carcinogenesis 3(3):341-344 1982

We have examined the fate of the asymmetric chromosomal distribution of DNA adducts generated by the chemical carcinogen r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE). Treatment of mouse embryo cells with BPDE results in 3.5x more binding to the linker DNA regions between nucleosome cores than to the nucleosome core DNA itself, but 24 hr post-treatment incubation of these cells leads to a loss of this non-random binding. A similar result was obtained when post-treatment incubation was carried out in the presence of hydroxyurea indicating that factors other than DNA replication are responsible for this change in adduct distribution. However in the case of excision repair deficient xeroderma pigmentosum (XP12/BE) cells the non-random adduct distribution was stable over a period of 48 hr, whereas with excision repair proficient XP variant (XP4/BE) cells, loss of preferential binding did occur. These results indicate that the loss of non-random nucleosomal DNA modification with time can be accounted for by the preferential removal of adducts from micrococcal nuclease sensitive linker DNA and further, demonstrates that in certain cells at least, the relative position of nucleosome core structures on DNA remains unchanged over a period of at least 48 hr. (Author abstract) (15 Refs)

31. NONCOVALENT BINDING OF 7BETA,8ALPHA-DIHYDROXY-9ALPHA,10ALPHA EPOXYTETRAHYDROBENZO[A]PYRENE TO DEOXYRIBONUCLEIC ACID AND ITS CATALYTIC EFFECT ON THE HYDROLYSIS OF THE DIOL EPOXIDE TO TETROL.

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Chemistry Dept., New York Univ., New York, NY, 10003
Biochemistry; 21(8):1864-1869 1982

In the presence of native DNA the hydrolysis of benzo[a]pyrene-7,8-diol 9,10-epoxide (BPDE) to tetrol's (BPT) is markedly accelerated (by a factor of up to approx 80 at 25 C, pH 7.0, in 5 mM sodium cacodylate buffer solution). When stopped-flow kinetic techniques are utilized, it is shown that the pseudo-first order hydrolysis rate constant KH is smaller by a factor of approx 3 in the presence of equivalent concentrations of denatured DNA, by a factor of 8-25 in the presence of nucleotides, and by a factor of 35-45 in the presence of nucleosides (depending on the nucleotide or nucleoside). In the presence of native DNA, KH increases with increasing DNA concentration and reaches a limiting value of KH = 0.684 +- 0.04 s-1 at DNA concentrations in excess of approx 5 x 10(-4) M (expressed in concentration of nucleotides). A kinetic model based on (1) rapid formation of a noncovalent BPDE-DNA complex followed by (2) slower hydrolysis of BPDE to BPT at these binding sites is consistent with the experimental data. It is shown furthermore that the DNA concentration dependence of KH and of noncovalent intercalative binding of BPDE to DNA is similar and that addition of magnesium ions (which is known to reduce intercalative binding of planar aromatic molecules to DNA) also reduces KH. These results suggest, but do not necessarily prove, that the DNA binding sites at which the hydrolysis of BPDE (to BPT) is catalyzed are intercalative in nature. (Author abstract) (36 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

32. THE INDUCTION OF CYTOCHROME P-448 DEPENDENT BENZO(A)PYRENE HYDROXYLASE IN SACCHAROMYCES CEREVISIAE.

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Biochem Biophys Res Commun; 105(3):1115-1121 1982

A form of cytochrome P450 with maximal absorption at 448 nanometers was induced in Saccharomyces cerevisiae grown in high glucose medium by benzo(a)pyrene (BP). The inability of BP to induce cytochrome P-448 in yeast grown in low glucose medium indicated that conditions similar to high glucose concentration may be required for cytochrome P-448 production. BP metabolism in yeast was also induced by dimethylnitrosamine and phenobarbital. 3-Methylcholanthrene induced a form of the enzyme with a higher affinity for BP. Addition of lanosterol to medium resulted in decreased affinity for BP. (18 Refs)

33. ULTRASTRUCTURAL CHANGES OF EPITHELIUM-CONNECTIVE TISSUE JUNCTION IN EXPERIMENTAL LINGUAL TUMORS.

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J Oral Pathol; 11(2):159-173 1982

The invasive nature of neoplastic epithelial cells during oral carcinogenesis was examined. Golden hamsters were subjected to trauma (scratching) of the tongue followed by 9,10-dimethyl-1,2-benzanthracene application for 16 wk. This procedure produced plaque like lesions, epithelial hyperplasia, and papillary invasive carcinoma, examined by light and electron microscopy. In plaque-like lesions, the basal lamina was partially reduced in both thickness and density or partially discontinuous. Various forms of cytoplasmic projections were observed at the portion of the basal cel near the intercellular space in epithelial hyperplasia. The basal lamina was absent around these cytoplasmic projections. In papillary invasive carcinoma, numerous cytoplasmic projections extended from various portions of the basal surface of the basal cells into the underlying connective tissue. The basal lamina was again absent around these cytoplasmic projections. In both epithelial hyperplasia and papillary invasive carcinoma, collagen fibrils in the connective tissue area around the cytoplasmic projections and islands were substantially reduced. Some fibroblasts in that connective tissue area contained many intracellular collagen fibrils. Some of the cytoplasmic projections appeared almost empty, some contained tonofilaments and ribosomes in small numbers, while others contained great numbers of ribosomes but lacked tonofilaments. (25 Refs)

34. BENZO(A)PYRENE-INDUCED EARLY CYTOPATHOLOGIC CHANGES AND PEROXIDASE ACTIVITY IN THE ENDOMETRIUM OF OVARIECTOMIZED RATS.

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Toxicol Appl Pharmacol; 63(2):248-256 1982

The compound benzo(a)pyrene (BP) (50 mg/kg/day sc once a day for 3-6 days) induced mitosis, peroxidase activity, and focal squamous cell metaplasia in the endometrial epithelium of ovariectomized rats. Diethylstilbestrol (DES) (20 ug/kg/day sc for 3-6 days) administered alone did not produce significant ultrastructural changes in the endometrial cells of castrated rats but did induce peroxidase activity. Concomitant administration of DES and BP induced significant cytopathological changes. Thus, BP alone can induce metaplasia in rat endometrium without the involvement of ovarian hormones, and DES may enhance the cytotoxicity of BP, apparently by stimulating uterine peroxidase activity that may be involved in the metabolic activation of BP. (33 Refs)

35. BIOLOGICAL CHARACTERISTICS AND ESTROGEN AND PROGESTERONE RECEPTORS IN MAMMARY CARCINOMA INDUCED IN MALE SPRAGUE-DAWLEY RATS BY A SERIES OF INTRAGASTRIC INTUBATIONS OF 7,12 DIMETHYLBENZ(A)ANTHRACENE.

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Cancer Res; 42(6):2434-2439 1982

Biological characteristics and estrogen (ER) and progesterone (PR) receptors were studied in male mammary carcinomas induced by 7,12-dimethylbenz(a)anthracene (DMBA) in male inbred Sprague-Dawley rats (MM). DMBA-induced carcinomas in females (MF) were used as controls. In 26 of 44 female rats given 20 mg DMBA once by gastric intubation at 50 days of age, MF with microscopic characteristics of cystic papillary adenocarcinoma developed 124 +-45 (S.D.) days after challenge. In all of the 42 male rats given 10 mg DMBA at 14 day intervals for 14 wk starting from 28 days of age, MM with microscopic characteristics of medullary adenocarcinoma developed 100 +-21 days after the first intubation of DMBA. The growth of primary MM was unaffected by orchiectomy or estrogen. Eighty to 100% of the MM transplanted in the four groups could grow in intact female rats, ovariectomized female rats, intact male rats, and castrated male rats, while the transplanted MF could grow only in intact female rats. The histology of MM was unchanged in primary and transplanted tumors under various hormonal conditions. ER were present in almost all of the hormone-independent primary and transplanted MM, although the levels for cytosol ER in MM were significantly lower than those in MF. Injection of 10 ug 17beta-estradiol induced marked synthesis of PR in primary and transplanted MM, even 24 and 48 hr after the 17beta-estradiol injection. These findings show that MM are hormone-independent but, like hormone-dependent female tumors, contain ER and estrogen-dependent PR. (Author abstract) (24 Refs)

36. INDUCTION OF HEPATIC MICROSOMAL PROPRANOLOL N-DESISOPROPYLASE ACTIVITY BY 3-METHYLCHOLANTHRENE AND SUDAN III.

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Biochem Biophys Res Commun; 105(3):1233-1239 1982

The cytochrome P448-dependence of propranolol metabolism was investigated. Propranolol metabolism was induced in Wistar rat liver (measured in microsomes) to three fold control values by 3-methylcholanthrene or sudan III, and 1.5-2 fold by phenobarbital. 7,8-Benzoflavone inhibited propranolol metabolism. It was concluded that N-desisopropylation, one of the major pathways of propranolol metabolism, is predominantly catalyzed by cytochrome P-448, or by one of the structural gene products of the arylhydrocarbon hydroxylase locus. (21 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

37. EFFECT OF VITAMIN A COMPOUNDS ON THE COVALENT BINDING OF BENZO(A)PYRENE TO NUCLEAR MACROMOLECULES.

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J Nutr Sci Vitaminol; 27(1):33-41 1981

Isolated liver nuclei from rats treated with 3-methylcholanthrene (20 mg/kg, ip) 24 hr previously were incubated with 3H- or 14C-labeled benzo(a)pyrene (BP: 1.0-9.7 uM) in the presence or absence of vitamin A compounds (1.2-122.0 uM). Retinol inhibited the covalent binding of BP to nuclear macromolecules. It markedly inhibited BP binding to the DNA and protein of the nuclear matrix, but had little effect on the labeling of bulk DNA and protein in the chromatin fractions. The inhibitory effects of retinol depended on its concentration and the time of its addition to BP-exposed nuclei. Retinal and retinyl acetate also strongly inhibited BP binding to nuclear macromolecules; retinoic acid was a less effective inhibitor. (17 Refs)

38. DMBA-INDUCED TUMORS AND THEIR PREVENTION BY AROMATIC RETINOID (RO 10-9359).

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Arch Dermatol Res; 272(1/2):37-47 1982

The protective effect of aromatic retinoid Ro 10-9359 (AR) against 7,12-dimethyl-benz(a)anthracene (DMBA) induced epithelial tumors was studied in rabbits under controlled systemic application of 30 mg AR (8-10 mg/kg body wt) by an esophageal tube 5 days/wk. AR dose had to be reduced to 20 mg because of toxic signs 25 days after onset of the study. Electron microscopic investigations were performed. First tumors in the auricles were observed at the end of 2 wk. One or several tumors were observed in the six animals after 8 or 9 wk of treatment. The tumors had the clinical appearance of human keratoacanthoma with a typical horn-filled crater. None of the animals treated with DMBA and AR developed tumors.

All 1 animals treated with AR suffered from inflammation and maceration of the pads. Ten animals underwent wt loss, eight showed hair loss and edematous swelling of the lips and nose. The section revealed exostoses at the insertion of the foot tendon symmetrically on both hind legs in 7/11 AR treated animals. The skin of the back of AR-treated animals was not significantly altered. The skin from the snout of the same animals showed exorbitant accumulation of fine granular material in the intercellular spaces of the upper epidermal layers. The epidermal cells of DMBA-treated and AR-protected animals showed 'cytoplasmic activation' consisting of an increase in the number of mitochondria, accumulation of RNA, pronounced Golgi zone, and enlarged and widended ergastoplasm, and less structural protein. A fine granular intercellular material, though in relatively sparse amount, and dyskeratotic bodies were also observed. (22 Refs)

39. ORAL MUCOSAL CARCINOGENESIS IN HAMSTERS: INHIBITION BY VITAMIN E.

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Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, 188 Longwood Ave., Boston, MA, 02115
JNCI; 68(5):791-797 1982

Eighty young adult male and female Syrian golden hamsters (Mesocricetus auratus) were divided into four equal experimental groups. In Group 1 animals the left buccal punch was painted 3x weekly with a 0.5% solution of 7,12-dimethylbenz[a]anthracene (DMBA) in heavy mineral oil. In Group 2 animals the left buccal pouch was similarly painted with DMBA, but the animals also received orally 10 mg vitamin E (dl-alpha-tocopherol) in peanut oil twice weekly on alternate days with the DMBA painting. Group 1 animals received a similar amount of peanut oil vehicle, Group 3 animals received only vitamin E (vitamin E controls) in peanut oil, and Group 4 animals served as untreated controls receiving only peanut oil. Four animals in each group (2 males and 2 females) were killed at 8, 10, 12, 14, and 16 wk. Buccal pouches were photographed and excised, and tumors were noted and measured in the left buccal pouches. In Group 2 animals receiving vitamin E, tumor formation was significantly delayed, so that by 14-16 wk there were fewer tumors and their av size was smaller than that of tumors in Group 1 animals that were painted with DMBA but received no vitamin E supplement. In Group 2 there was also less invasion of underlying tissues and less surface necrosis. (Author abstract) (30 Refs)

40. BILE ACIDS: EIFECTS ON ABSORPTION OF 1,2-DIMETHYLHYDRAZINE AND 7,12-DIMETHYLBENZ[A]ANTHRACENE IN THE COLON OF THE RAT AND GUINEA PIG.

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Dept. Surgery, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
JNCI; 68(4):619-622 1982

The specific effects of bile acids as cocarcinogens were investigated. Absorptions of [14C]7,12-dimethylbenz[a]anthracene, [14C]dimethylhydrazine ([14C]DMH), and [3H]inulin from loops of colons from outbred Sprague-Dawley rats and Hartley guinea pigs were determined. In each animal absorption of one carcinogen and inulin was studied in one control loop and in a experimental loop containing either deoxycholic acid (DOC) or chenodeoxycholic acid (CDOC). DOC had a more pronounced effect on increasing loss of carcinogen from the intestinal lumen than did CDOC. This role of bile acids was consistent with their known effect of increasing intestinal permeability. Less carcinogen remained in the colon mucosa when DOC was present in the intestinal lumen. Although [14C]DMH was absorbed more rapidly from the intestinal lumina of guinea pigs than from those of rats, the rat accumulated more of the carcinogen in the intestinal mucosa and liver. (Author abstract) (16 Refs)

41. MODIFICATION OF BENZO[A]PYRENE-INDUCED TRANSFORMATION OF C3H/10T1/2 CELLS BY PREGNENOLONE-16ALPHA-CARBONITRILE AND DEXAMETHASONE.

Kimyai G, Somogyi A, Lagenbach R
Eppley Inst. for Res. in Cancer and Allied Diseases, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE. 68105
Cancer Lett; 15(3):215-221 1982

The effect of microsomal enzyme inducers, pregnenolone-16alpha-carbonitrile (PCN) and dexamethasone (DEX), on benzo[a]pyrene (BP)-induced transformation of C3H/10T1/2 cells is described. Data for benz[a]anthracene (BA) cytotoxicity and transformation which was used as a control, are presented. PCN increased the toxicity of BP and also increased the BP-induced transformation in a dose-dependent manner. Max enhancement of transformation occurred at 52 uM PCN and was 250% of the BP alone treated culture. DEX caused a dose-dependent reduction in BP-induced cellular transformation. Max reduction (65%) was observed at 23 uM DEX. DEX pretreatment also reduced the cytotoxic effect of BP. DEX treatment alone was not cytotoxic. The simultaneous treatment with DEX did abolish the toxic effect of BP, while PCN did not statistically alter BP toxicity. Both PCN and DEX only slightly induced aryl hydrocarbon hydroxylase (AHH) activity in the cells after a 24-hr treatment. The induction was maximal at approx 0.23 uM for DEX and 2.5 uM for PCN. The induction was much lower than that observed for BA. The greatest difference in metabolism of BP by pretreated C3H/10T1/2 cells occurred at 8-12 hr after the addition of BP. By 24 hr the amount metabolized in control and pretreated cells is nearly equivalent. Results suggest that a correlation between the ability of PCN and DEX to induce AHH activity or BP metabolism to water soluble products and their ability to alter transformation is not entirely consistent. (20 Refs)

42. POLYAMINE BIOSYNTHESIS AND SKIN TUMOR PROMOTION: INHIBITION OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE-PROMOTED MOUSE SKIN TUMOR FORMATION BY THE IRREVERSIBLE INHIBITOR OF ORNITHINE DECARBOXYLASE ALPHA-DIFLUOROMETHYLORNITHINE.

Takigawa M, Verma AK, Simsiman RC, Boutwell RK
McArdle Lab. Cancer Res. Univ. Wisconsin, Madison, WI, 53706
Biochem Biophys Res Commun; 105(3):969-976 1982

Topical application of alpha-difluoromethylornithine (DFMO) to shaved mouse skin or administered in the drinking water in conjunction with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), inhibited the formation of 7,12-dimethylbenz(a)anthracene-initiated skin papillomas. Application of 10 nanomoles of TPA to mouse skin led to a rapid and transient induction of epidermal ornithine decarboxylase (ODC) activity. Application of 1.37 umoles DFMO 1 hr after TPA to mouse skin inhibited ODC induction by nearly 100%. DFMO also resulted in significant inhibition of induced and basal levels of putrescine, while spermidine-induction was inhibited by only 20%. DFMO administered in the drinking

water (1% wt/vol) beginning 3 days before and continuing through the experimental period inhibited TPA-induced increases in ODC by 100%, basal putrescine levels by 40%, and induced putrescine levels by 90%; spermidine levels were somewhat decreased, but spermine levels remained unchanged. DFMO inhibited the formation of DMBA-initiated and TPA-promoted skin papillomas by 50% when administered on the skin and by 90% when administered in the drinking water. These results indicate an essential role for the products of ODC in TPA promotion of carcinogenesis. (22 Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

43. TUMOR-INITIATING ABILITY OF THE TWELVE MONOMETHYLBENZ[A]ANTHRACENES.

Wislocki PG, Fiorentini KM, Fu PP, Yang SK, Lu AY
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Carcinogenesis; 3(2):215-217 1982

The 12 possible monomethylbenz[a]anthracenes (MBAs) were examined for their tumor-initiating activity in the classical two-stage initiation-promotion experiment. Based on the average number of tumors/mouse, 7-methylbenz[a]anthracene was the most tumorigenic compound of the series causing 4.9 papillomas/mouse at an initiating dose of 400 nmol/mouse. At this same dose level 8-MBA and 12-MBA was equally potent causing 1.6 papillomas/mouse. 5-and 9-MBAs caused approx 0.6 papillomas/mouse at this dose level. These data are in general agreement with previous experiments using other model systems. Of interest is the low tumorigenicity of the 1-, 2-, 3- and 4-MBAs which has been cited in support of the bay region theory of polycyclic aromatic hydrocarbon carcinogenesis. The tumor-initiating ability of anthracene and 9,10-dimethylanthracene was also examined. Neither of these compounds possessed tumor-initiating activity (Author abstract) (25 Refs)

44. INDUCTION OF HEPATIC TUMORS WITH 7,12-DIMETHYLBENZ[A]ANTHRACENE IN TWO SPECIES OF VIVIPAROUS FISHES (GENUS POECILIOPSIS).

Schultz ME, Schultz RJ
Biological Sciences Group, Univ. Connecticut, Storrs, CT. 06268
Environ Res; 27(2):337-351 1982

Live neoplasms were induced in two species of viviparous fishes, Poeciliopsis lucida and P monacha, by repeated short-term exposures to an aqueous suspension of 5 ppm 7,12-dimethylbenz[a]anthracene (DMBA). Predominantly hepatocellular neoplasms developed in 47 out of 106 fish surviving the period allowed for tumor development, 6-9 mo after initial exposure to DMBA. The use of short-term exposure periods of 6 hr in young fish and up to 20 hr in adults reduced stress and mortalities caused by the toxicity of DMBA at 5 ppm. A lower concentration of DMBA, 0.25 ppm, failed to induce tumors in any of the surviving 230 of 295 young fish administered repeated 20-hr exposures. This study shows for the first time that DMBA is carcinogenic to fish. (Author abstract) (8 Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

45. CARCINOGENIC EPOXIDES OF BENZO[A]PYRENE AND CYCLOPENTA[CD]PYRENE INDUCE BASE SUBSTITUTIONS VIA SPECIFIC TRANSVERSIONS.

Eisenstadt E, Warren AJ, Porter J, Atkins D, Miller JH
Dept. Microbiology, Harvard Sch. Public Health, Boston, MA, 02115
Proc Natl Acad Sci USA; 79(6,part1):1945-1949 1982

We have determined the spectrum of base-pair substitution mutations induced in the lacI gene of uvB- strain of Escherichia coli by two polycyclic aromatic hydrocarbons, (+-)7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE), and 3,4-epoxycyclopenta[cd]pyrene (CPPE). Approximately 10% of all lacI mutations induced by either BPDE or CPPE are nonsense mutations, suggesting that base-pair substitutions are a large fraction of the mutational events induced by these agents in the uvB- bacteria. Both carcinogens specifically induced the G-C to T-A and, to a lesser extent, the A-T to T-A transversions. One possible mechanism for transversion induction at G-C sites by BPDE might involve carcinogen binding to the exocyclic amino group of guanine in the template strand followed by a rotation of the modified base around its glycosylic bond from the anti to the syn conformation. This could allow specific pairing of modified base with an imino tautomer of adenine. (Author abstract) (26 Refs)

46. RELATIONSHIP BETWEEN THE YIELD OF SISTER CHROMATID EXCHANGES AND CHEMICAL STRUCTURE OF THE MUTAGEN.

Selezneva TG, Shatalina IG, Chesnokov AN
Inst. Medical Genetics, Moscow, USSR
Genetika; 18(2):269-274 1982

The relationship between the yield of sister chromatid exchanges (SCE) and the chemical structure of the mutagen was studied in cultured chinese hamster cells. The cells were incubated with 12 different alkylating agents. All mutagens were found to produce a dose-dependent increase of the yield of SCE. The highest incidence of SCE was observed after incubation with benzoquinone derivatives. (13 Refs) (In RUS)

47. MUTAGENICITY OF SUBSTITUTED CARBAZOLES IN SALMONELLA TYPHIMURIUM.

LaVoie EJ, Briggs G, Bedenko V, Hoffmann D
Div. Environmental Carcinogenesis, Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Mutat Res; 101(2):141-150 1982

Mutagenic activities of several substituted carbazoles in Salmonella typhimurium TA1535, TA1537, TA1538, TA98, and TA100 were compared. Of all possible isomers of methylcarbazole, only 9-methylcarbazole was mutagenic when assayed in S typhimurium TA100 in the presence of S9. Other dimethylcarbazoles in which one of the methyl substituents was in the 9-position were similarly assayed for mutagenic activity; with the exception of 1,9-dimethylcarbazole, each of the compounds were mutagenic in TA100 with activation. The mutagenic potency of the dimethylcarbazoles was less than that of 9-methylcarbazole. All of the carbazole derivatives were inactive as mutagens in TA1535, TA1537, TA1538, and TA98, with or without S9 mix. Substitution at the 9-position of carbazole re-

sulted in a loss of mutagenic activity. Metabolism studies performed with 9-methylcarbazole confirmed that 9-hydroxymethylcarbazole is a major metabolite and proximate mutagen. It was suggested that the mutagenicity of 9-hydroxymethylcarbazole is related to the release of formaldehyde, a hypothesis supported by the lack of mutagenic activity of 9-formylcarbazole and 9-acetylcarbazole. (17 Refs)

48. METABOLIC ACTIVATION OF 3-METHYLCHOLANTHRENE AND BENZO(A)PYRENE TO MUTAGENS IN THE L5178Y/TK ASSAY BY CULTURED EMBRYONIC RODENT CELLS.

Amacher DE, Paillet SC, Zelljadt I
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Environ Mutagen; 4(2):109-119 1982

Early passage cultured rodent cells [Crl;COBS CD(SD) BR rats, Crl;COBS CD1 (ICR) BR mice, Ela ENG/SYR hamsters] were used for the activation of 3-methylcholanthrene (3MCA) and benzo(a)pyrene (B(a)P) in the mouse lymphoma L5178Y/TK mutation assay. S9 mix prepared from cells of the same rodent lines was used for comparison. Both B(a)P and 3MCA were mutagenic when tested with 5% (vol/vol) S9 from all three sources, but were negative in the L5178Y/TK mutation assay without S9. When tested with three different primary mouse embryo cultures B(a)P was negative, but 3MCA was reproducibly positive. Responses were similar with rat embryo cultures. Both B(a)P and 3MCA gave positive results with hamster embryo monolayers; for 3MCA the SHE X and SHE-48 sources were used. Cell contact between the lymphoma cells and the hamster cells was studied with the use inverted microscopes. A mutagenesis assay using intact hamster cells for the metabolic component and L5178Y cells as targets is evidently feasible. (34 Refs)

49. MORPHOLOGICAL TRANSFORMATION OF C3H/10T1/2 CL8 CELLS BY PROCARCINOGENS.

Oshiro Y, Balwierz PS
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Environ Mutagen; 4(2):105-108 1982

Transformation of C3H/10T1/2CL8 cells was attempted using two 3-day periods of exposure to aflatoxin B1 (AFB1), benz(a)anthracene (BAA), 4-nitroquinoline-1-oxide (4NQO), beta-naphthylamine (BNA), and 2-acetylaminofluorene (2AAF) at various concentrations, with replenishment of the medium between the two exposures and during the final 3 days of exposure. Exogenous activation was not used. Transformation was determined according to the criteria of Reznikoff et al. AFB1, BAA, and 4NQO exhibited both Type II and Type III foci sufficiently to indicate detection of morphological transformation. BNA treatment yielded too few Type II foci for a conclusive result, and no Type III foci; 2AAF induced only 1 Type II focus, indicating a negative result. Simply modifying the 10T1/2 transformation method by increasing the exposure from 1 day to 6 days can increase the sensitivity to some procarcinogens that require metabolic activation. (7 Refs)

50. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

Abe S, Sasaki M
(c/o Sasaki) Chromosome Res. Unit, Faculty Science, Hokkaido Univ., North 10, West 8, Sapporo, Hokkaido 060, Japan
Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell lines by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1 steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-6 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

51. ANAPHASE ABERRATIONS: A MEASURE OF GENOTOXICITY IN MUTAGEN-TREATED FISH CELLS.

Kocan RM, Landolt ML, Sabo KM
Dept. Pathology, SM-30, Univ. Washington, Seattle, WA, 98195
Environ Mutagen; 4(2):181-185 1982

A continuous culture line of rainbow trout gonad (RTG-2) cells was exposed to benzo(a)pyrene (BAP), 3-methylcholanthrene (3MC), anthracene, 1-naphthol, 9-aminoacridine (9AA), mitomycin C (mit-C), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). During exposure cells were examined for the presence of abnormalities in chromosome arrangement of anaphase figures during mitosis, and were compared to the effects of only solvent (dimethylsulfoxide). Both BAP and 3MC elevated the number of anaphase abnormalities, with more effect at 48 hr than at 24 hr. MNNG, mit-C, and 9AA were also effective in increasing the number of abnormalities. Abnormalities included mainly attached fragments, acentric fragments and bridges, with some side-arm bridges and multipolar cells. Toxicity and inhibition of cell division were also observed with all compounds. No increase in chromosomal lesions was observed in cells treated with naphthol or anthracene, suggesting that each chemical's characteristics, not the chemical class to which it belongs, are important in mutation induction. The in vitro RTG-2 cell system has a highly active mixed function oxygenase system, which eliminates the need for microsomal supplement. This test system is comparable to the Ames test and the sister-chromatid exchange test in sensitivity for measuring chromosome damage. (38 Refs)

52. LACK OF ASSOCIATION BETWEEN INDUCTION OF DOMINANT-LETHAL MUTATIONS AND INDUCTION OF HERITABLE TRANSLOCATIONS WITH BENZO(A)PYRENE IN POSTMEIOTIC GERM CELLS OF MALE MICE.

Generoso WM, Cain KT, Hellwig CS, Cacheiro NL
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 94(1):155-163 1982

Benzo(a)pyrene (BP) was tested for its ability to induce dominant-lethal mutations in germ cells of (101 x C3H)F1 male mice. A dose of 500 mg/ml BP, which inhibits the ability of male mice to mate, was administered ip in a single injection. Serial matings indicated dominant-lethal effects in the intervals 4.5-5.5 and 6.5-7.5 days, corresponding to early and middle spermatozoa, and possibly in the intervals 32.5-33.5 and 34.5-35.5 days, corresponding to prelototene spermatocytes. Dominant lethal effects were clear-cut in matings in the interval 3.5-7.5 days after treatment. The yield of BP-induced dominant-lethal effects in these stages was also affected by the stock of untreated females used, possibly due to the differential ability of fertilized eggs to repair BP-induced lesions in the fertilizing sperm. Of the total 548 male progeny analyzed from two stocks of mothers, only one was found to be a carrier of a reciprocal translocation. These results indicate that BP is effective in inducing dominant lethal mutations but relatively ineffective in inducing heritable translocations in male postmeiotic germ cells. (9 Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

53. REACTIONS OF THE K-REGION EPOXIDES OF POLYCYCLIC AROMATIC HYDROCARBONS WITH PHOSPHODIESTERS. A POTENTIAL DETOXIFICATION REACTION.

Di Raddo P, Chan TH
Dept. Chemistry, McGill Univ., Montreal, Quebec H3A 2K6, Canada
J Org Chem; 47(8):1427-1431 1982

Phenanthrene 9,10-oxide reacts with diethyl hydrogen phosphate to give 9-phenanthrol. The reaction was first order in both epoxide and phosphate concentrations, with a pseudo-first-order rate constant k psi= 4.2 x 10(-1) mol l L e-t. Similarly, chrysene 5,6-oxide on reaction with phosphate opened regiospecifically to give 6-chrysenol. Several anilinium phosphate salts were prepared and reacted with phenanthrene 9,10-oxide. The extent of reaction was markedly influenced by the pKa of the anilinium salt. The biological implications of this study in understanding the relative noncarcinogenicity of K-region arene oxides are discussed. (Author abstract) (30 Refs)

54. DETERMINATION OF 6 POLYCYCLIC AROMATIC HYDROCARBONS ACCORDING TO THE DRINKING WATER REGULATION ON A SPECIAL C18-REVERSE PHASE COLUMN: DEPENDENCE OF RETENTION UPON TEMPERATURE, DETECTION LIMIT OF UV-ABSORBANCE, SELECTION OF MOBILE PHASES.

Fischer R
Analytik, D-ZAA, BASF- Aktiengesellschaft, D-6700 Ludwigshafen/Rhein W. Germany
Fresenius Z Anal Chem; 311(2):109-111 1982

According to the drinking water regulation, the total concentration of six polycyclic aromatic hydrocarbons (PAH) should not exceed 0.25 ug/liter (l). This can be achieved with the aid of a relatively simple high process liquid chromatography system. A special C18-reverse phase column (available commercially) was used with methanol or acetonitrile as the mobile phase, and the PAH were measured at 254 nanom by means of a UV spectrophotometer. Detection limit was 0.007 ug/l for the sum of all six PAH. Since retention is dependent on temperature , exact and constant temperature should be used and reported. (15 Refs) (In GER,

55. DETERMINATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN VEGETABLE OILS BY CAFFEINE COMPLEXATION AND GLASS CAPILLARY GAS CHROMATOGRAPHY

Kotarovic L, Trattler H
Nestle Res. Dept., P.O. Box 88, CH-1814 La Tour-de-Peilz, Switzerland
J Chromatogr; 237(2):263-272 1982

Glass capillary gas chromatography was used for the determination of polycyclic aromatic hydrocarbons (PAHs). Reproducible PAH profiles were obtained from vegetable fats and oils by complexing them with caffeine in formic acid solution. The caffeine-complexable materials were then separated by column liquid and thin-layer chromatography, respectively. Glass capillary gas chromatographic results for PAHs specified by the US Environmental Protection Agency were obtained after split injection within about 25 min. Quantitative and qualitative results are given for several commercial vegetable oils. Recoveries of PAHs were in the range 68-95%. The detection limit was 16 ng of coronene in 100 g of oil. Grapeseed oil was shown to contain the lowest 'polycyclic aromatic hydrocarbons burden'. (Author abstract) (35 Refs)

REVIEWS AND OTHER RELATED STUDIES

56. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL

Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:183-185 1981

Carcinogenicity of environmental benzo(a)pyrene (BAP) is reviewed. bAP is a polycyclic aromatic hydrocarbon consisting of five aromatic rings that is formed during combustion of fossil fuels; the compound is the most important carcinogen in soot, cigarette smoke, coal gasification effluent, and coke oven emissions. Three sources are expected to increase atmospheric

levels due to energy/fuel conservation: stationary combustion of coal and synthetic fuels and increased use of diesel fuel by automobiles. The primary route of human exposure to BAP is inhalation, where the compound is deposited in the lower lung and eluted into surrounding tissue. Most carcinogens are thought to act through strong electrophilic metabolites which bind covalently to DNA of the lung. Animal data indicate that the action of BAP is enhanced by other chemicals such as sulfur dioxide and other irritant gases. A threshold dose for BAP has not been found; the effect of small doses of BAP may be greater than that for a single high dose. Mixtures containing BAP (urban air, industrial emission, cigarette smoke) result in increased carcinogenic effect. Since the early 1970's BAP has tested positive in 20 in vitro short term test systems considered predictive for human carcinogenicity/mutagenicity. Quantitative risk assessment for BAP is confounded by problems in extrapolating high doses in small animal studies to low doses in humans and by the variables involved in monitoring data. (186 Refs)

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Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
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2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163- 85 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY 12208
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5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Munro NB
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Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction Available from National Technical Information Service, Springfield, VA, as DE81027859., 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
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10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
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DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Schrijver M, Tytgat GN
Dept. Internal Medicine, Div. Gastroenterology, Univ. Amsterdam, 1 e Helmerstraat 104, 1054 EG Amsterdam, The Netherlands
Neth J Med; 25(2):49-55 1982

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Kritchevsky D
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14. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.
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15. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.
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17. SKIN CANCER. OCCUPATIONAL CAUSES.
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Rom WN, Lee JS, Craft BF
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Buffler PA, Aase JM
Sch. Public Health, Univ. Texas Health Science Center at Houston, P.O. Box 20186, Houston, TX, 77025
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Kotin P
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23. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.
Hull LA
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27. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.
Elias Z, Cavelier C
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Polycyclic Aromatic Hydrocarbons and Related Compounds

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. POLYCYCLIC AROMATIC HYDROCARBONS IN ONTARIO FOUNDRY ENVIRONMENTS.

Verma DK, Muir DC, Cunliffe S, Julian JA, Vogt JH, Rosenfeld J, Chovil A

Occupational Health Program, McMaster Univ., Hamilton, Ontario, Canada

Ann Occup Hyg; 25(1):1-25 1982

Polycyclic aromatic hydrocarbon (PAH) and metal concentrations were assessed in ferrous and nonferrous foundry environments. Max concentrations of various PAH compounds, including suspected carcinogens, ranged from 0.09-12.92 umole/cubic meter (m3) and 9.48-26.59 umole/m3 in personal and area sampling, respectively. The threshold limit values for iron,

HE 20.3173/2:

lead, and copper were exceeded 1, 2, and 3x, respectively, in 126 samples. Significant variation in PAH concentration could not be correlated with various foundry occupations. Higher concentrations of PAH were discovered in ferrous than in nonferrous foundrys. (26 Refs)

2. ANALYSIS OF POLYCYCLIC AROMATIC HYDROCARBONS IN MUSSELS (MYTILUS GALLOPROVINCIALIS) FROM THE THERMAIKOS GULF, GREECE.

Iosifidou HG, Kilikidis SD, Zamarianos AF
Dept. Food Hygiene, Aristotelian Univ., Thessaloniki, Greece
Bull Environ Contam Toxicol; 29(5):535-541 1982

Gas chromatographic analysis of mussels of the Thermaikos Gulf, an area known to be contaminated with petroleum hydrocarbons, showed that the mussels are contaminated with 17 polycyclic aromatic hydrocarbons (PAH). These included the following carcinogenic compounds: benzo(a)pyrene, benzo(a)anthracene, dibenzo(a,c)anthracene + dibenzo(a,h)anthracene, dibenzo(a,l)pyrene, dibenzo(a,i)pyrene, and TP + CH. The concentrations of total PAH and carcinogenic PAH in the mussels were 9 and 19 nanog/g wet wt, respectively. A positive correlation was shown between the levels of total PAH and carcinogenic PAH in mussels and industrial activity in two different areas of the gulf. (13 Refs)

3. LUNG CANCER IN FOUNDRIES (MEETING ABSTRACT)

Gibson ES
Occupational and Environmental Health, DOFASCO, Inc., Hamilton, Ontario, Canada
J Occup Med; 24(4):331 1982

Certain foundry trades, have been associated with an excess risk for lung cancer for many years. Only in the past few years have epidemiological studies been used to attempt to clarify the situation. Four studies tend to support this finding; one study, part of a much larger study, does not. Casual agents have not been identified, but polycyclic aromatic hydrocarbons emitted in moulding are generally blamed. The epidemiological evidence for the association of lung cancer with foundry work will be reviewed. Results of work done at DOFASCO using the Ames test to identify mutagenic activity in the foundry atmosphere will be described. Levels of mutagenic activity correlate with the differences in risk between the foundry trade groups will be studied. Ongoing work in testing for chromosomal aberrations, urine mutagenicity, chemical identification of carcinogens, and the examination of the role of particulate matter as a carrier of carcinogenic material will be described. (no Refs)

4. CARCINOMA OF THE RESPIRATORY TRACT AFTER OCCUPATIONAL EXPOSURE TO TAR: A CRITICAL OMISSION FROM THE LIST OF OCCUPATIONAL DISEASES.

Manz A
Monckebergstrasse 8, im Hause der HWW, D-2000 Hamburg 1, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Prophyl Ergon; 32(4):118-127 1982

Current lists of occupational diseases maintained by the Federal Republic of Germany and other European countries attribute only the skin disorders to the occupational exposure to coal tar. Exposure is considered to be limited to workers in coke plants. However, other workers, such as road repair crews who use tar, are also exposed. Recognition of occupational hazards affects the practice of occupational medicine, effort at prevention, and measures to humanize the workplace. Legal requirements for reporting of job-related diseases include mucosal changes or carcinogenesis in the urinary bladder as a criterion. Since anthracite coal tar and pitch contain compounds such as beta-naphthylamine, workers exposed to these substances should be covered by appropriate regulations. However, the presence of known carcinogens in coal tar and pitch is apparently not widely known. Studies in several countries have shown an increased incidence of cancers of the respiratory tract and urinary bladder among gas works employees when compared to nonexposed workers such as office workers and water works employees. Smoking apparently affects the incidence of cancers among nonexposed workers but not among exposed workers. Current evidence therefore indicates that respiratory and bladder cancers should be included on the lists of occupationally related diseases. (61 Refs) (In GER)

5. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.

Chaklin AV, Gritsiute LA
No affiliation given
Vopr Onkol; 28(2):3-9 1982

Literature data on the role of smoking and environmental pollutants in the etiology of lung cancer (LC) are reviewed. Epidemiological studies showed the relationship between the smoking and incidence of LC. LC morbidity in 45-64 yr old men increased from 1.4 per 100,000 for nonsmokers to 5.9 for those who smoked 5 cigarettes/day, 13.5 for those who smoked 6-10 cigarettes/day, 29.5 for those who smoked 25-56 cigarettes/day, and 47.4 for those who smoked greater than 56 cigarettes/day. Carcinogenicity of tobacco tar is associated with the presence of polycyclic hydrocarbons, N-nitrosamines, vinyl chloride, phenols, and various co-carcinogens. Recent studies showed the carcinogenic effect of 'passive' smoking. Increased LC morbidity in the regions with intensive chemical industry indicates the co-carcinogenic effect of such air pollutants as sulfur dioxide. Pathogenesis of LC is associated with the history of chronic lung inflammation, tuberculosis, scleroderma, exposure to asbestos, immunologic suppression, and individual activity of aryl hydroxylase. (45 Refs) (In RUS)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

6. BENZO(A)PYRENE METABOLISM AND ENTEROHEPATIC CIRCULATION IN THE RAT.

Chipman JK, Hirom PC, Frost GS, Millburn P
Dept. Biochemistry, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Adv Exp Med Biol 136(partA):761-768 1982

Enterohepatic circulation of benzo(a)pyrene (BP) metabolites were investigated in rats to determine the availability of potentially toxic metabolites to tissues within this cycle. [14C]-BP (3 uM/kg, 25 uCi/kg or 35 uCi/kg) was administered by iv injection to rats with bile duct cannulae. For enterohepatic recirculation experiments, 2-hr bile samples were collected from anesthetized rats receiving the [14C]-BP. The bile samples containing the [14C] BP metabolites were cross-transfused into the

duodena of bile fistulated rats, and the bile was collected from the recipients. Metabolites from the the bile samples were separated by high pressure liquid chromatography. The major identified metabolites in the bile extract were conjugates and/or polyhydroxylated metabolites. BP 4,5-diol, 9-OH BP, and 3-OH BP/BP 3,6-quinone; the proximate carcinogen benzo(a)pyrene 7,8-diol was not detected in these experiments. When biliary metabolites were cross-transfused to the duodena of bile duct cannulated rats, 18.7 ± 6.5% of the dose was re-excreted in the bile within 30 hr. The pattern of metabolites which had been recycled from duodenum to bile was very similar to that in the bile which had been infused. Metabolite A1 (unknown) was, however, only detected after recirculation of metabolites; this metabolite was found to increase in relative amount in the bile of rats where there was minimal interference to the enterohepatic circulation. As the process of enterohepatic circulation necessitates the transfer of biliary metabolites, which are mutagenic, though the intestinal wall, it is possible that the metabolites or their secondary products could react with nucleophilic sites in the intestinal wall. (13 Refs)

7. IN VIVO METABOLISM OF 3-METHYLCHOLANTHRENE (MC) IN PREGNANT C57BL/6 AND DBA/2 MICE (MEETING ABSTRACT)

George JD, Vaier S, Warshawsky D
Department of Environmental Health, University of Cincinnati, Cincinnati, OH
Toxicologist; 2(1):25 1982

MC has been linked to carcinogenesis in laboratory animals and their transplacentally exposed offspring. Activation of MC to reactive intermediates is catalyzed by microsomal aryl hydrocarbon hydroxylase (AHH), the activity of which correlates positively with tumorigenesis. This study compares the in vivo metabolic profiles of MC in the maternal and fetal tissues of C57BL/6 (high AHH) and DBA/2 (low AHH) mice. Maternal liver, placenta and whole fetuses from pregnant mice exposed to 14C-MC were evaluated for extractable and bound 14C activity. HPLC (high performance liquid chromatography) analyses of ethylacetate extracts revealed no qualitative differences in the spectrum of metabolites found in the tissues of either strain of mouse; seven metabolites, in addition to MC, have been identified. In both strains, the placenta appears to be acting as a reservoir for the parent compound. The free MC metabolite profiles of the two strains of mice differ quantitatively for all tissues studied. Tissues from DBA/2 mice contained higher relative levels of MC, which is consistent with the lower AHH activity of this strain. Two additional regions of 14C activity have been tentatively identified through HPLC and alumina column chromatography as conjugates of the free metabolites. In the non-extractable tissue residue from both strains, the 14C activity was primarily associated with the lipid and protein fractions, although some activity was associated with RNA, DNA, glucosaminoglycan, and carbohydrate. Findings to date indicate that the major difference in the metabolic profiles of MC in C57BL/6 and DBA/2 mice is in the level of metabolism and not in the types of metabolites produced. (no Refs)

8. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA

Juchau MR, Chao ST, Namkung MJ
Dept. Pharmacology, Sch. Medicine, SJ-30, Univ Washington, Seattle, WA, 98195
Adv Exp Med Biol; 136(partA):555-573 1982

Studies concerning the capacity of placental tissues to biotransform and bioactivate polycyclic aromatic hydrocarbons (PAH) and the placental enzyme systems that catalyze these reactions are reviewed. PAH which undergo enzymically catalyzed monooxygenation in placental tissues include: benzo(a)pyrene (BaP), 7,12-dimethylbenz(a)anthracene (DMBA), N-2-fluorenylacetamide (FAA), 3-methylcholanthrene (3MC), chrysene, benzo(e)pyrene, dibenz(a,h)anthracene and benz(a)anthracene. For each of these substrates, hydroxylation rates are increased by preexposure of the maternal organism to 3MC, but not to phenobarbital-type inducers. Placental enzymes can catalyze the conversion of at least three of these substrates (DMBA, BaP and FAA) to reactive intermediates. Recent studies indicate that a number of P-450 cytochromes that are not specially detectable with current methods are responsible for the limited bioactivation observed. 3MC- and phenobarbital-inducible monooxygenases also catalyze the conversion of estrogens to catechol estrogens in placental tissues of humans and experimental animals. The in vivo significance of these observations remains to be clarified. (52 Refs)

9. METABOLISM OF BENZO(A)PYRENE AND BENZO(A)PYRENE 4,5-OXIDE IN RABBIT LUNG.

Boyd JR, Smith BR, Ball LM, Plummer JL, Wolf CR, Philpot RM, Devereux TR, Fouts JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Adv Exp Med Biol; 136(partA):511-524 1982

Various investigations trying to elucidate some of the metabolic factors that can contribute to the polycyclic aromatic hydrocarbon (PAH)-mediated toxicity in the rabbit lung are described. The PAH used in the studies included benzo(a)pyrene (bP) and benzo(e)pyrene 4,5-oxide (BPO), and a stable K-region arene oxide metabolite of BP, as substrates. In the rabbit, unlike rodents, only minor changes in the rate of BP turnover occur in lung microsomes treated with either 3-methylcholanthrene or phenobarbital. Both microsomal epoxide hydrolase and cytosolic glutathione transferase activities are much lower in rabbit lung than in liver. The metabolism of BP by purified rabbit pulmonary cytochromes P-450 is discussed. Studies of the metabolism of BPO by perfused rabbit lung are described which indicate that equivalent amounts of arene oxides will cause less damage/toxicity in those organs or cells with higher detoxification activity. Studies with perfused lung and liver indicate that BPO is not reduced in vivo. Metabolism of BP and BPO by cells isolated from rabbit lung is discussed. In a recent study, epoxide-metabolizing activities were measured in isolated, sonicated rabbit pulmonary cell fractions, containing varying proportions of Clara and alveolar Type II cells. When BPO was used as the substrate, specific epoxide hydrolase activity was highest in those fractions which contained the greatest proportion of Clara cells. This result was not unexpected since cytochrome P-450 also is preferentially localized in this cell type. (27 Refs)

10. THE METABOLIC ACTIVATION OF SOME POLYCYCLIC HYDROCARBONS: THE ROLE OF DIHYDRODIOLS AND DIOL-EPOXIDES.

Sims P
Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, Japan
Adv Exp Med Biol; 136(partA):487-500 1982

The role of dihydrodiols and diol-epoxides as reactive intermediates in the process by which polycyclic aromatic hydrocarbons induce cancer were discussed. The discussion was based on studies on the metabolic activation of three typical polycyclic hydrocarbons, the active carcinogen 7-

methylbenz(a)anthracene (7-MBA), and the relatively weak carcinogens benz(a)anthracene (BA) and dibenz(a,c)anthracene (DBA). The metabolic activation of 7-MBA appears to involve one or both isomers of the 'bay region' diol-epoxide, 3,4-dihydrodiol 1,2-oxide. On the other hand, the roles played by the 3,4-dihydrodiol 1,2-oxide and 8,9-dihydrodiol 10,11-oxide in the metabolic activation of BA are not yet clear. Both the 3,4-and 8,9-dihydrodiols are metabolites of BA in mouse skin and both appear to be further metabolized to diol-epoxides. In the metabolism of DBA, the 1,2-and 3,4-dihydrodiols, which might give rise to vicinal diol-epoxides on further metabolism, also exist in quasi-diaxial conformations and thus may not yield these reactive intermediates. Overall, the mechanisms involved in the metabolic activation of DBA are still unclear. (38 Refs)

11. HIGHLY TUMORIGENIC BAY-REGION DIOL EPOXIDES FROM THE WEAK CARCINOGEN BENZO(C)PHENANTHRENE.

Jerina DM, Sayer JM, Yagi H, Croisy-Delcey M, Ittah Y, Thakker DR, Wood AW, Chang RL, Levin CW, Conney AH
Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD, 20205
Adv Exp Med Biol; 136(partA):501-523 1982

The bay-region theory proposing that diol epoxides of carcinogenic polycyclic aromatic hydrocarbons would have the highest biological activity when they were on angular benzo-rings and when the epoxide group was part of the bay-region was studied with respect to diol epoxides of benzo(c)phenanthrene (BcP), which has an unusually hindered bay-region. Mutagenicity of BcP derivatives in bacteria and mammalian cells was studied, either for inherent mutagenic activity or activity on metabolic activation. In bacterial tests with metabolic activation, the most active compound was the 3,4-dihydrodiol with the bay-region 1,2-double bond, exhibiting 4-fold more activity than BcP and approx 10-fold more activity than the other dihydrodiols tested. In tumorigenicity studies, the 1,2-and 5,6-dihydrodiols were inactive, while the 3,4-dihydrodiol with a bay-region 1,2-double bond was almost 2x as active as BcP. These results strongly implicate bay-region diol epoxides as ultimate carcinogenic metabolites of BcP. On mouse skin, the diol epoxide-1 and diol epoxide-2 diastereomers had similar tumorigenic activity, which was unexpectedly high; approx 15x more active than benzo(a)anthracene 3,4-diol-1,2-epoxide-2, previously the most active diol epoxide tested on mouse skin. A sound basis for the unusually high biological activity of these diol epoxides is currently not available. Some unique feature of the shape of BcP may account for the remarkable biological activity of its bay-region diol epoxides and the high degree of crowding in the bay-region of BcP may be a contributing factor. (46 Refs)

12. MICROSOMAL METABOLISM OF 8-FLUOROBENZO[A]PYRENE (MEETING ABSTRACT)

Chou MW
National Center for Toxicological Research, Jefferson, AR, 72079
Fed Proc; 41(3):973 1982

Fluorobenzo[a]pyrene (8-FBP) is a more potent mutagen than benzo[a]pyrene (BP) in Salmonella typhimurium tester strain TA 98 and TA 1538 with S9 or microsome activation. Metabolism of 8-FBP by rat liver microsomes was studied to elucidate the activation pathways. The major metabolites formed were purified by high performance liquid chromatography and identified as 3-hydroxy-8-FBP, 3,x-dihydroxy-8-FBP and 8-FBP- trans-4,5-dihydrodiol by the analyses of uv, mass and nmr (nuclear magnetic resonance) spectra. The circular dichroism spectrum of 8-FBP-trans-4,5-dihydrodiol was similar to that of BP-4R,5R-dihydrodiol, a metabolite of BP, indicating that 8-FBP-trans-4,5-dihydrodiol also has a 4R,5R absolute configuration. The results suggest that a fluoro substituent at C-8 of BP (1) can inhibit the enzymatic oxidation at the 7,8-and 9, 0-positions but (2) does not change the stereospecificities of the cytochrome P-450 enzymes and of epoxide hydrolase for 8-FBP-trans-4R,5R-dihydrodiol formation. The results also suggest that 8-FBP-4,5-oxide, the precursor of 8-FBP-trans-4,5-dihydrodiol, may be an ultimate mutagenic metabolite of 8-FBP. (no Refs)

13. MODULATION OF EPOXIDE HYDROLASE ACTIVITY. EFFECT ON THE ACTIVATION OF BENZO[A]PYRENE AND ITS COVALENT BINDING TO DNA IN THE NUCLEUS.

Guenthner TM, Oesch F
Dept. Pharmacology, Univ. Mainz, D-6500 Mainz, W. Germany
Adv Exp Med Biol; 136(partA):705-716 1982

Role of epoxide hydrolase (EH) in binding 7,8-dihydrodiol-9,10-oxide (DDO) and 9-hydroxy-benzo(a)pyrene-4,5-oxide (HBPO) to DNA was investigated using isolated rat liver nuclei. EH levels were moderated using trans-stilbene oxide (TSO) and trichlorpropilene oxide (TCPO). Male Sprague-Dawley rats were treated with 3-methylcholanthrene (MC) and/or TSO. Patterns of modified nucleosides obtained from incubation of nuclei with 3H-benzo(a)pyrene (BP) are presented. When purified EH in 10-fold excess of the amount present in the nuclei was added to the incubation medium the degree of H3PO binding was diminished in the controls. Similar results were obtained when nuclei from MC plus TSO-treated rats were used. Results of experiments using nuclei and 7.5 mg of microsomal protein from MC-treated rats were very similar to those obtained using nuclei alone, except that the total binding of both BP metabolites was higher. The amount of HBPO binding was lower when the EH activity was increased, but binding of DDO was not changed. When EH was inhibited by TCPO, DDO binding decreased and HBPO increased. Individual pathways of BP metabolism are presented. Results showed that the levels of EH activity greatly influence the amounts and patterns of BP-derived metabolites binding to DNA, and imply that EH activity is an important factor in influencing the in vivo carcinogenicity of BP and other polycyclic hydrocarbons. (35 Refs)

14. REGIO- AND STEREOSELECTIVITY OF HEPATIC CYTOCHROME P-450 TOWARD POLYCYCLIC AROMATIC HYDROCARBON SUBSTRATES.

Thakker DR, Levin W, Yagi H, Conney AH, Jerina DM
Lab. Bioorganic Chemistry, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD, 20205
Adv Exp Med Biol; 136(partA):525-539 1982

Some aspects of the regio- and stereoselectivity of hepatic cytochrome P-450 (CP) toward selected polycyclic aromatic hydrocarbons (PAH) substrates are discussed. The compounds include: benzo(a)pyrene [B(a)P], benzo(e)pyrene, phenanthrene (PH), benzo(a)anthracene [BA], chrysene [CH], and dibenzo(a,h)anthracene [DBA]. The following areas are explored: substrate specificity of the CP toward PAH substrates, stereoselectivity in the formation of dihydrodiols, and metabolism of dihydrodiols to diol epoxides. Among conclusions drawn, it is noted that PH is metabolized most efficiently whereas CH and DBA are turned over much more slowly. The cytochrome P-450 system and epoxide hydrolase favor

formation of dihydrodiols with R,R configuration. The predominant enantiomers of the dihydrodiols with the bay-region double bond as well as bay-region diol epoxides derived from PH, CH, BA and B(a)P, are superimposable when their bay-regions are aligned. These metabolically favored isomers of the dihydrodiols and bay-region diol epoxides are also the more carcinogenic isomers when derived from carcinogenic PAH. (30 Refs)

15. STUDIES ON THE MECHANISM OF STIMULATION OF MICROSOMAL H2O2 FORMATION AND BENZO(A)PYRENE HYDROXYLATION BY SUBSTRATES AND FLAVONE.

Hildebrandt AG, Bergs C, Heinemeyer G, Schlede E, Roots I, Abbas-Ali B, Schmoldt A
Institut fur Klinische Pharmakologie der Freien Universitat Berlin, Klinikum Steiglitz, Hindenburgdamm 30, D-1000 Berlin 45, W Germany
Adv Exp Med Biol; 136(partA):179-198 1982

The effects of substrates of microsomal hepatic mixed function oxidase cytochrome P-450 (CP450) on microsomal NADPH-dependent H2O2 formation, mechanism proposed for the interaction of substrate and NADPH in the activation of H2O2 formation, and the possible contribution of H2O2 to the in vitro activation of mixed function oxidation reaction are discussed. Modification by activators rather than by 'uncouplers' causes increases in NADPH oxidation, H2O2 formation, and hydroxylation reaction. Increased interaction of reductase and CP450 is at least as much responsible as 'uncouplers' for the increase in H2O2 formation. Microsomes were incubated with increasing concentrations of NADPH and hexobarbital or flavone to investigate the effects of activators. Results indicated that optimal H2O2 formation requires the stoichiometric presence of both NADPH and substrate. Changes in substrate-NADPH concentration alter the concentration of the functionally active complexes, and thereby the oxidase activity. The effect of inversely varied ratios of NADPH and flavone on benzo(a)pyrene (BP) metabolism was investigated. Maximal BP hydroxylation was obtained when flavone was high and NADPH low. Direct contribution of H2O2 in the metabolism of BP to phenolic metabolites might explain the observed difference. The maximal effects of flavone on BP hydroxylation suggest that the magnitude of electron flow appears to be important for the participation of either monooxygenase reactions, favored at high NADPH concentrations, or peroxidatic reactions, prevalently operative at low NADPH, but high flavone concentrations. (45 Refs)

16. ROLES OF UDP-GLUCURONOSYLTRANSFERASE IN THE INACTIVATION OF BENZO(A)PYRENE.

Bock KW, Bock-Hennig BS, Lilienblum W, Pfeil H, Volp RF
Dept. Pharmacology and Toxicology, Univ. Gottingen, D-3400 Gottingen, W. Germany
Adv Exp Med Biol; 136(partA):53-73 1982

Functional heterogeneity of uridine-5' diphosphate-glucuronosyltransferase (UDP-GT), coordinate induction of 3-methylcholanthrene-inducible forms of cytochrome P-450 and UDP-GT, and roles of UDP-GT in the metabolism of benzo(a)pyrene (BP) are discussed. On the basis of alterations of liver microsomal UDP-GT activity four groups of substrates can be distinguished. Tissue distribution of UDP-GT activities in microsomal fractions from different rat organs are presented. At least two functionally heterogenous forms of UDP-GT can be distinguished in rats and mice. UDP-GT1 and UDP-GT2 are characterized by differential induction of groups conjugation reactions by 3-methylcholanthrene and phenobarbital, respectively, and by separation and purification of these enzyme forms to apparent homogeneity. UDP-GT1 and UDP-GT2 activities show different developmental patterns and tissue distributions. UDP-GT1 shows high activity towards 3-hydroxybenzo(a)pyrene and BP-7,8-dihydrodiol. The conjugation of these intermediates may explain why in the presence of uridine-5'-phosphate-glucuronic acid, BP-monooxygenase activity is stimulated and BP mutagenicity in the Ames test (TA98) is decreased. The importance of conjugation reactions in the inactivation of BP metabolites is also observed in rat liver perfusion studies with BP when conjugation reactions are inhibited by salicylamide (SA). Mutagenicity in the medium is significantly increased under these conditions. In the absence of SA mutagenicity is low, suggesting efficient inactivation of BP by the liver. (45 Refs)

17. DNA DAMAGE, REPAIR AND DMBA METABOLISM IN HUMAN FETAL CELLS (MEETING ABSTRACT)

D'Ambrosio SM, Gibson-D'Ambrosio RE, Orawec C, Leong Y, Chang D
Department of Pharmacology and Radiology, College of Medicine, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1559 1982

The level of DNA damage, repair and replication following UV irradiation and N-ethyl-N-nitrosourea (ENU) treatment as well as the binding and metabolism of 7,12-dimethylbenz(a)anthracene (DMBA) was quantitated and compared in vitro in cells derived from human fetal brain, dermis, kidney, liver, intestine and lung. Using UDS (unscheduled DNA synthesis) as a measurement of DNA repair, fetal brain, kidney and liver cells exhibited lower (30-60%) levels of UDS than did fetal dermal, lung or intestinal cells treated with UV radiation or ENU. The order for repair of UV induced DNA damage was: dermal greater than lung greater than intestinal greater than kidney greater than liver greater than brain cells. The order for UDS following ENU treatment was: lung greater than dermal greater than intestinal greater than brain greater than liver cells. Intestinal cells metabolized DMBA approximately 30%, while brain cells metabolized only 2.6% of the DMBA. Liver, dermal, lung and kidney, metabolized 5-10% of the DMBA during a 48 hour period. Using HPLC (high pressure liquid chromatography), qualitative as well as quantitative differences in the metabolite profiles were observed in each cell culture. The level of DMBA binding to cellular DNA was of the order: intestinal greater than lung greater than liver greater than dermal greater than kidney cells. These studies provide, important information as to how various human fetal organs metabolize DMBA, repair DNA damage and replicate new DNA followirg carcinogen exposure. (no Refs)

18. DIETARY SELENIUM, HEPATIC ARYLHYDROCARBON HYDROXYLASE AND MUTAGENIC ACTIVATION OF BENZO(A)PYRENE, 2-AMINOANTHRACENE AND 2-AMINOFLUORENE.

Gairola C, Chow CK
Tobacco and Health Res. Inst., Lexington, KY, 40506
Toxicol Lett; 11(3/4):281-287 1982

Young (5-6 wk old) and adult (66 wk old) male Sprague Dawley rats were maintained on a low selenium (Se) basal diet with or without 1 or 2 ppm Se supplement for 5 or 20 wk. Five days prior to sacrifice, the animals were injected ip with Aroclor to determine aryl hydrocarbon hydroxylase (AHH) inducibility. Using the Ames Salmonella/microsome mutagenicity assay, the activation potential of the liver postmitochon-

(rial supernatant was determined using benzo(a)pyrene (BP), 2-amino-fluorene (2AF) and 2-acetyl aminofluorene (2AAF) as potential mutagens. Low dietary Se caused a reduced AHH level in young control rats but dietary Se had no effect on AHH inducibility in both dietary groups. Since Se is a cofactor for glutathione peroxidase (GSH-P), the levels of GSH-P were decreased more in young rats by low dietary Se. Dietary Se did not appreciably affect the activation of BP, while low dietary Se affected the mutagenic activation of 2AF and 2AAF. (24 Refs)

BINDING TO CELLULAR MACROMOLECULES

19. COVALENT BINDING OF METABOLICALLY ACTIVATED HYDROCARBONS TO SPECIFIC MICROSOMAL PROTEINS.

Jergil B, Schelin C, Tunek A
Biochemistry 1, Chemistry Centre, Univ. Lundt, S-220 07 Lundt 7, Sweden
Adv Exp Med Biol; 136(partA):341-346 1982

Binding specificity of benzene (BZ), chlorobenzene (CB), 3-methylcholanthrene (MCH), and benzo(a)pyrene (BP) to rat liver microsomal protein (MP) after metabolic activation was examined. The examined compounds bound covalently to MP in a NADPH-dependent manner indicating that metabolic activation was required for binding. Reduced glutathione inhibited binding. The binding patterns to MP examined by SDS-polyacrylamide gel electrophoresis and fluorography were quite similar for metabolic activated BZ, CB, and phenol. The binding patterns to liver microsomes from phenobarbital (PB)- or MCH-treated rats did not differ significantly from those of control animals. The binding patterns for BP and MCH were distinctly different from those of BZ, phenol, and CB. The binding of these compounds to microsomes from MCH-treated rats was much higher than that to microsomes from control or PB-treated animals. Seven BP metabolites were isolated and incubated with NADPH and microsomes from control or pretreated rats. All isolated metabolites, including BP-4,5-oxide, had to be metabolically activated to bind covalently. Variations were found among the metabolites in extent and specificity of binding. Of the isolated metabolites tested, BP-7,8-dihydrodiol bound most efficiently after metabolic activation, particularly to microsomes from MCH-treated rats. Results suggested that the binding pattern, at least in part, is determined by the mechanism of metabolic activation. (33 Refs)

20. PHYSICAL BINDING OF DIOL-EPOXIDE DERIVATIVES OF THE CARCINOGEN BENZO(A)PYRENE TO DNA (MEETING ABSTRACT)

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Fed Proc; 41(3):698 1982

Two metabolically-formed, diol-epoxide derivatives of the strong carcinogen benzo(a)pyrene [B(a)P], 7,8-dihydroxy-9,10-oxy-7,8,9,10-tetrahydro benzo(a)pyrene (BPDE) and 9,10-dihydroxy-7,8-oxy 7,8, 9,10-tetrahydro benzo(a)pyrene (reverse-BPDE), have been implicated in covalent binding to nuclear proteins in hamster embryo cells treated for 24 hr with B(a)P. However, only BPDE binds to DNA in treated cells. We have used the characteristic bathochromic shift in the absorbance spectra of polycyclic aromatic hydrocarbon DNA intercalation complexes to probe the in vitro physical interactions of BPDE and reverse BPDE with purified DNA. Both diol epoxides form intercalation complexes with similar association constants and intercalation is blocked by low concentrations of Mg++. In addition, the rate of hydrolysis of BPDE and to a lesser extent of reverse BPDE, is enhanced by DNA. This enhancement of hydrolysis is blocked by low concentrations of Mg++ suggesting the involvement of intercalation complexes in the mechanism of enhanced hydrolysis. Thus, the apparent lack of covalent binding of reverse-BPDE to DNA in cell cultures is not due to an inherent inability to physically interact with DNA. (no Refs)

21. EFFECT OF HISTONE ACETYLATION ON THE FORMATION AND REMOVAL OF B(A)P CHROMATIN ADDUCTS.

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Nucleic Acids Res; 10(9):2775-2789 1982

The modification of core histone proteins in mouse 10T1/2 cells and human lung epithelioid (A549) cells by B(a)PDE ((+-)7a,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene) in vivo and in vitro was found to be similar. Only histone H2A and H3 were extensively modified. Also other proteins, possibly A24 protein and the minor histone H1 species seem to be binding relatively high levels of the ultimate carcinogen. Butyrate treatment which causes hyperacetylation of the core histones, did not change the specificity of B(a)PDE binding to core histones, nor did it affect the initial level of DNA modification. The acetylated species of histone H3 were all accessible to B(a)PDE, suggesting that these epsilon-amino-groups of the lysine residues are not the targets of the B(a)PDE. The rate of removal of B(a)P-DNA adducts was not affected by butyrate treatment in either normal human or XP fibroblasts. Furthermore, the B(a)P-core histones were not preferentially removed from normal human fibroblast chromatin during a 24 hr post-treatment incubation. (Author abstract) (50 Refs)

22. IN VITRO CARCINOGENESIS IN CANINE BLADDER (MEETING ABSTRACT)

Klaunig JE, Constantini MG, Barut BA, Goldblatt PJ
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71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

As part of our overall investigation of mechanisms of bladder carcinogenesis we have developed methods for establishing primary and secondary cultures of canine bladder urothelial cells. Urinary bladders from adult dogs of mixed breed were removed immediately after exanguination. Four pieces of bladder (0.5 x 0.5 cm) were placed urothelium side up per 60-mm culture dish. Two milliliters of Ham's 15l culture medium were added per dish, and dishes were maintained at 36.5 C in a humidified CO2 incubator. Epithelial cells were seen extending from the explants 2 to 3 days after culture initiation. Within 2 to 3 weeks cells were almost confluent on the culture dish. The inclusion of fetal bovine serum in the medium resulted in the overgrowth of epithelial cultures by fibroblasts. The calcium concentration in the medium had a significant influence on differentiation and growth of primary urothelial cells. A concentration of 1 x 10(-4) M calcium appeared optimal for cell growth and prevention of differentiation. Secondary cultures

were initiated by trypsinization of primary cultures. Fetal bovine serum was required in the medium for secondary culture cell growth. DNA repair (measured by inductor of unscheduled DNA synthesis (UDS) was evident in explants, primary, and secondary cultures following exposure to methylnitrosourea, aflatoxin B1, 4-aminoipheayl, and benzo(a)pyrene. UDS in each compound displayed a linear dose response. Radiolabeled benzo(a)pyrene was metabolized and covalently bound to DNA in bladder explants primary and secondary cultures. (no Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

23. OOCYTE DESTRUCTION BY BENZO(A)PYRENE AND OXYGENATED DERIVATIVES (MEETING ABSTRACT)

Mattison DR, Nightingale MS
NICHD, National Institute of Health, Bethesda, MD
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982

Benzo(a)pyrene (BP) destroys oocytes in a time, dose, strain and species dependent fashion, and has been implicated in ovarian carcinogenesis and infertility. BP is not directly ovotoxic, but requires metabolism to an ultimate ovotoxin(s). These experiments were designed to explore possible metabolic pathways by comparing ovotoxicity of BP and 10 oxygenated derivatives in C57BL/6N (B6) and DBA/2N (D2) mice. Weanling B6 and D2 mice were treated with a single intraperitoneal injection of BP or oxygenated derivative (1, 10, 50, or 100 mg/kg) dissolved or suspended in corn oil. Mice were sacrificed 14 days later, ovaries removed, fixed, oocyte number determined, and ED50's for oocyte destruction calcaluated. ED50's for 3-hydroxybenzo(a)pyrene, 6-hydroxybenzo(a)pyrene, 7-hydroxybenzo(a)pyrene, and 9-hydroxybenzo(a)pyrene were less than 100 mg/kg in both strains. The 2-hydroxybenzo(a)pyrene was more ovotoxic than BP with ED50's of 2 and 6 mg/kg in B6 and D2 mice. BP-4,5-Oxide, trans-and cis-4,5-dihydrodiols, had ED50's greater than 100 mg/kg in both strains. BP 7,8-oxide was less ovotoxic than BP, but the trans-7,8-dihydrodiol was more ovotoxic with ED50's of 2 and 6 mg/kg in B6 and D2 mice. As 2-hydroxy BP does not appear to be produced in vivo, BP-7,8-dihydrodiol is the only proximate ovotoxin among the 10 tested derivatives, suggesting that BP-7,8-dihydrodiol-9,10-oxide is an ultimate ovotoxin. (no Refs)

24. EPIDERMAL-DERMAL JUNCTION DURING EXPERIMENTAL SKIN CARCINOGENESIS AND COCARCINOGENESIS AS REVEALED BY SCANNING ELECTRON MICROSCOPY.

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J Invest Dermatol; 78(5):395-401, 1982

During epidermal carcinogenesis important changes in the epidermal-dermal junction take place. Because of the methodological difficulties many of these changes, especially those concerned with three-dimensional organization of the junction, remain unsatisfactorily investigated. To obtain new information, we studied with scanning electron microscopy (SEM) the development of carcinogenic changes in the epidermis of mice induced by DMBA-TPA, (9,10-dimethyl 1,2 benzanthracene-12-O-tetra-decanoyl-phorbol-13-acetate) DMBA alone, and by the cocarcinogen TPA alone. We correlated the results with those from transmission electron microscopy and light microscopy. Although the epidermal changes morphologically showed similarities, biologically they differed. With them, distinct changes in the epidermal-dermal junction developed, that could be followed through early, hyperplastic and neoplastic phases. With the SEM the first changes were seen in the basal layer of the epidermis and concerned the cell arrangement. SEM provided information about the localization and development of incipient epidermal carcinomas induced by DMBA-TPA and DMBA treatment, as well as about the changes in the basal lamina. These can be classified by their surface, their extent and their frequency throughout large regions. Our studies indicate that these changes vary greatly, depending upon the treatment used and the time of their development. Only the progressive disintegration of the basal lamina is characteristic of carcinogenesis. (Author abstract) (32 Refs)

25. EFFECTS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE ON THYMUS CORTEX IN THE RAT. A MORPHOLOGICAL AND HISTOMETRICAL ANALYSIS.

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Virchows Arch [Cell Pathol]; 39(2):125-136 1982

In the rat, administration of 7,12-dimethylbenz(a)anthracene (DMBA) causes necrosis of the inner layers of the adrenal cortex and provokes rising levels of plasma cortisol. Histological and ultrastructural study of the thymus demonstrates a profound depletion of small thymocytes, especially in the inner cortex where they normally represent the greater part of the cell population. The thymic weight, and the cortico-medullary ratio as measured by histometry, decrease significantly. These findings are similar to those observed following steroid administration. However, whereas after steroid treatment restitution of the normal complement of thymocytes occurs within 7-10 days, in the present model the thymic weight and cortico-medullary ratio remain at the low levels observed on Days 1 and 3 until after Day 24 following DMBA administration. A block in the regenerative process is confirmed by the results of morphometrical analysis of the thymocyte nuclear area in the cortex. On Day 1 and 3 after DMBA the mean thymocyte nuclear area is reduced in the outer cortex and increased in the inner cortex, because of the selective destruction of small thymocytes and the migration of the steroidoresistant blast thymocytes towards the medulla. Subsequently, until after Day 24 the mean nuclear area of the thymocytes is significantly higher in the outer and in the inner cortex of treated rats than in the corresponding parts of the cortex of control rats. This aspect of the cortex is characteristic of the early phase of the regenerative process, ie of Day 2 or 3 after steroids administration. It can be assumed that in this experimental mode the thymic changes are due not only to the raised cortisol level but also to a direct effect of DMBA on the thymus, which is probably an inhibition of DNA synthesis in cells in the S phase of the mitotic cycle, ie in the replication of DNA. It also seems possible that a causal relationship exists between inhibition of DNA synthesis in proliferating organs like the thymus, and the carcinogenic activity of DMBA. (Author abstract) (35 Refs)

26. CYTOCHEMICAL STUDY OF RNA IN CELLS OF ANTERIOR PITUITARY GLAND OF RATS WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) INDUCED MAMMARY GLAND CARCINOMA.

Ganina KP, Iarushko AG
Inst. Problems Oncology, Kiev, USSR
Tsitol Genet; 16(1):3-6 1982

The functional activity of the anterior pituitary gland (APG) was studied in albino female rats subjected to iv administration of 7,12-dimethylbenz(a)anthracene (DMBA: 2 mg/day). Animals were sacrificed on days 10 and 40 after the termination of DMBA administration, and after the appearance of first palpable tumors of the mammary glands. Cytomorphological examination of the APG showed enhanced vascularization, progressive increase of the number of basophilic cells, and significant decrease of the number of acidophilic cells. The RNA content in the cytoplasm of basophilic cells showed decrease (from 1.51 units in controls, to 1.40 on day 10, 1.47 on day 40, and and 1.33 in tumor-bearing animals). RNA content in the nucleoli of basophilic cells was 1.01, 0.78, 0.87, and 0.76 units, respectively. Development of mammary gland tumors was associated with increase of RNA content in the cytoplasm and nucleoli of acidophilic cells. (15 Refs) (In RUS)

27. USE OF EPITHELIAL WHOLE-MOUNTS AND GAMMA-GLUTAMYL TRANSPEPTIDASE HISTOCHEMISTRY FOR EARLY QUANTITATION OF PRESUMPTIVE PRECANCEROUS FOCI IN HAMSTER BUCCAL POUCH (MEETING ABSTRACT)

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International Conference on Safety Evaluation and Regulation, of Chemicals, February 24-26, 1982, Boston, Massachusetts Bio-Research Institute; 1982

Biweekly topical application of the potent carcinogen dimethylbenz(a)anthracene (DMBA) to the buccal pouch of Syrian hamster results in the rapid induction of microscopic tests of basal cells rich in gamma-glutamyl transpeptidase (GGT) activity. The GGT-rich sites can be detected histochemically and quantitated in large full-thickness whole-mounts of pouch epithelium harvested as early as 3 days after beginning DMBA treatment. The earliest GGT-rich sites thus detected are individual cells and cell doublets. The number and size of the GGT-rich sites increases with successive DMBA applications. Interruption of DMBA treatment results in rapid loss of GGT activity However the persistence of the carcinogen-altered cell populations can be demonstrated by resuming DMBA application, resulting in 'reexpression' of GGT after and 11-week treatment-free interval. GGT can also be detected histochemically in a significant proportion of DMBA-induced hamster buccal pouch tumors. Full-thickness whole-mounts may be useful for the histochemical detection and quantitation of carcinogen-induced precancerous cells in this squamous epithelium. (no Refs)

28. EFFECTS OF TOBACCO SMOKE COMPOUNDS ON THE CILIARY ACTIVITY OF THE EMBRYO CHICKEN TRACHEA IN VITRO

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Toxicology; 23(1):41-55 1982

Chicken embryo trachea was exposed in vitro to one of 316 compounds representative of the gaseous and semivolatile phases of tobacco smoke, and time to complete ciliostasis was used as a measure of ciliotoxicity. All compounds were examined at one concentration (5 millim), and exposure time was fixed at 1 hr. Forty-nine percent of the compounds inhibited ciliary activity within 30 min (36% within 15 min), while 48% caused no ciliostasis within 60 min. Alkylated phenylethers, benzonitriles, benzaldehydes, phenols, benzenes, naphthalenes and indoles, or alpha, beta-unsaturated ketones and aldehydes or C6-C10 aliphatic alcohols, aldehydes, acids, and nitriles were ciliotoxic, whereas most benzoic acids, esters, polyaromatic hydrocarbons, amines, and N-heterocycles (except indoles) were not. It was concluded that tobacco smoke contains ciliotoxic compounds that could cause acute or chronic damage to ciliated epithelia. (27 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

29. INHIBITION OF DIMETHYLBENZANTHRACENE-INDUCED TUMORS IN RATS BY STRESS (MEETING ABSTRACT)

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Fed Proc; 41(3):1559 1982

Previous reports have indicated that various types of physical and psychological stressors inhibit the growth of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumors in Sprague-Dawley (S-D) rats. Dopamine (DA) stimulated adenylate cyclase activity in the caudate nucleus has been claimed to be inversely associated with spontaneous mammary tumors in mice. We tried to replicate some of these findings and investigate some factors likely to be involved in this inhibition. Female S-D rats were used for induction of tumors by DMBA. Rats subjected to daily sessions of immobilization 5 days a week for 9 weeks showed a significant decrease in tumor weight when compared with non-stressed rats; 2.7g vs 5.4g per rat, N-20. Housing animals individually significantly increased the size of tumor over group-housed animals, 13.9g vs 5.0g per rat, N-20. However, rats bred for high versus low plasma catecholamine levels in response to stress did not differ in the weight of their tumors. No difference was seen in the number of tumors in any of these groups. Behavioral testing of emotionality prior to DMBA exposure showed no correlation to later tumor formation DA-stimulated adenylate cyclase activity was found to be lower in animals which are more susceptible to tumor induction, 107 vs 142%, N-11. Short term immobilization stress had no effect on this DA stimulated adenylate cyclase activity. (no Refs)

30. FURTHER STUDIES ON THE INHIBITION OF CHEMICAL CARCINOGENESIS BY CORYNEBACTERIUM PARVUM

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Cancer Immunol Immunother; 12(3):259-265 1982

Effects of both single and repeated injection of Corynebacterium parvum (CP) on the incidence of fibrosarcoma in response to methylcholanthrene (MC) were studied in adult female (17-22 g) mice of strains CBA and BALB/c. The carcinogen was administered by sc or ip implantation of an MC-

impregnated Millipore disc. In CBA mice, repeated iv injection of CP starting on day-4 (0.7 mg every 4 wk, or 0.35 every 2 wk) significantly delayed appearance of sarcomas after sc injection of 0.5 mg MC on day 0; repeated injection of CP starting on day 24, and a single injection of CP on day-4, 6, 20, or 28, had no significant effect. In BALB/c mice, repeated injection of CP starting on day-4 or +6 significantly delayed the appearance of sarcomas after sc injection of 0.25 mg MC, and some significant inhibition occurred even when repeated administration of CP was started on day 41. After implantation of a 5% MC-wax disc sarcomas developed in 8 of 8 untreated CBA mice but in only 13 of 21 CBA mice which received repeated iv injections of CP (0.35 mg every 2 wk starting on day-4, 6, or 20). In BALB/c mice sc implanted 0.5% MC-wax discs were extruded in 4 of 16 mice which received repeated iv injections of CP; in the remaining 12 mice sarcomas developed somewhat later than in untreated mice but the difference was not statistically significant. When MC-wax discs were implanted ip, repeated injections of CP from day-4 completely prevented the development of tumors, irrespective whether the disc was attached to the liver or elsewhere in the peritoneal cavity. Sc implantation of 0.1 mg MC discs resulted in the development of fibrosarcomas in nearly all untreated mice, and the time for tumors to develop was independent of the pore size of the disc. The pore size did, however, affect the response to CP. With discs of 0.22 micrometer pore size the development of sarcomas appeared to be somewhat delayed by repeated injection of CP starting before disc insertion, but the difference was not quite significant at the $P = 0.05$ level. (12 Refs)

31. MODULATION OF MICROSOME-MEDIATED BENZO[A]PYRENE-METABOLISM BY SERUM.

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Carcinogenesis; 3(4):359-362 1982

The effects of serum on the metabolism of benzo[a]pyrene (BP) by liver microsomes from 3-methylcholanthrene-treated rats were studied. In the presence of serum, the aryl hydrocarbon hydroxylase activities were enhanced to 160-570% of the control value. Enhancement of BP-metabolism by serum was also revealed by high performance liquid chromatography, but the relative amounts of a series of BP-metabolites were not changed appreciably by addition of serum. Binding of BP-metabolites to DNA was influenced by serum: adducts derived from two stereo-isomeric BP-7,8-dihydrodiol-9,10-oxides were increased, while those from 9-hydroxybenzo[a]pyrene-4,5-oxide were reduced. (Author abstract) (18 Refs)

32. CAFFEINE AND UNSATURATED FAT DIET SIGNIFICANTLY PROMOTES DMBA-INDUCED BREAST CANCER (MEETING ABSTRACT)

Minton JP, Foecking MK, Abou-Issa H
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Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Caffeine is an important causative agent in the development of human fibrocystic breast disease. The epithelial proliferation resulting from caffeine consumption has been shown to be reversible when caffeine abstention is carried out. The exposure of a well-established animal model to the known carcinogen dimethylbenz(a)anthracene (DMBA) is associated with the development of a hormone sensitive estrogen receptor positive breast tumor in nearly 90% of the animals. To determine the possibility of caffeine being an extraordinary promoter of breast cancer development in animals consuming vegetable fat the following study was carried out. A controlled study comparing the time to tumor development and the number of tumors and the growth rate of breast cancer in Sprague-Dawley rats which had been given 50 mg of DMBA at 6 weeks of age compared the tumor promotional effects of caffeine alone, caffeine and unsaturated fatty acids in combination, unsaturated fatty acids alone, and a standard rat chow diet. Twenty rats were in each group. The results show that the rat which consumed caffeine and unsaturated fatty acids had the earliest development of tumor, the most multiple tumor occurrence, and the most rapid rate of growth. Average time to development was 94 days. The fat and water rats had an average time of development of 133 and 140 days respectively. The caffeine alone rats had a mean time to tumor development of 188 days. The combination of an unsaturated fat diet and caffeine significantly shortened the time to tumor development when compared with the other three groups. (no Refs)

33. EFFECTS OF DIETARY PROTEIN ON RELEASE OF OVARIAN STEROIDS AND DEVELOPMENT OF DMBA-INDUCED BREAST TUMORS IN RATS (MEETING ABSTRACT)

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Department of Research, Mercy Hospital and Medical Center, Chicago, IL, 60616
Fed Proc; 41(3):290 1982

Virgin rats were fed 8%, 19.5% or 31% isocaloric protein diets for a period of 3 weeks before mating. The diets were maintained throughout the mating, gestation and lactation periods. After weaning, all pups were continued on their respective diets and ate ad libitum during the entire experimental period. DMBA (dimethylbenzanthracene) was administered intragastrically at dose of 3mg/100 g body weight at the age of 3 weeks after vaginal opening. Serum estradiol and progesterone were measured at the time of DMBA administration and 6 months after DMBA treatment. Six months after DMBA 30% in 8%, 48% in 19.5%, and 73% in 31% protein diet rats exhibited breast tumors. Estradiol was significantly less in 8% protein group at 3 weeks after vaginal opening, as compared to the same stages of estrous cycle of 19.5% or 31% protein group; progesterone was significantly lower in 8% protein group at diestrous and proestrous afternoon as compared to those of high protein groups. There was no difference in estradiol and progesterone among these 3 groups of rats at 6 months after DMBA treatment. These data indicate that the lower incidence of DMBA-induced breast tumors in lower protein diets rats may be partly due to the low ovarian hormone profile at the time of DMBA exposure. (no Refs)

34. STIMULATION OF DRUG AND CARCINOGEN METABOLISM BY PROLONGED ORAL TOBACCO CONSUMPTION.

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Biochem Pharmacol; 31(8):1595-1597 1982

Oral administration of tobacco to rats for 21 days caused remarkable stimulation of the metabolism of phenacetin, aniline and benzo[a]pyrene, a carcinogen, by hepatic microsomal mixed function oxidases (MFO). Such treatment for 6 days resulted in a small increase in the activities of phenacetin O-deal-

kylase and aromatic hydrocarbon hydroxylase (AHH) without affecting aniline hydroxylase activity. Nicotine given orally was found to be a relatively weak inducer of phenacetin O-dealkylase and aniline hydroxylase, and elicited a maximum increase in their activities within 6 days which remained unchanged even after 21 days of continuous administration. However, these two enzyme systems were not affected following only one or two doses of tobacco and nicotine. Both tobacco and nicotine inhibited these biotransformations in vitro. (Author abstract) (15 Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

35. INCIDENCE AND TYPE OF TUMORS INDUCED BY ORAL DMBA IN NK CELL DEFICIENT C57BL BG/BG MICE, +/BG LITTERMATES AND H-2 CONGENIC STRAINS OF B10 OF VARYING NK ACTIVITY (MEETING ABSTRACT)

Cochran AJ, Argov S, Karre K, Klein GO, Klein G
Departments of Pathology and Surgery, The Center for Health Sciences, University of California, Los Angeles, CA, 90024
9th International RES Congress, February 7-12, 1982, Davos Switzerland. American Reticuloendothelial Society 68 pp., 1982.

To study the effect of the beige mutation on chemical carcinogenesis, 64 C57Bl bg/bg mice and 83 +/bg littermate controls received 5 weekly intrasgastric doses of DMBA (dimethylbenzanthracene). We examined the incidence and histological types of tumors that developed. By 165 days after first DMBA contact 18% of +/bg, and 31% of bg/bg mice developed tumors. Beige mice had a higher incidence of epithelial and non-epithelial tumors in cutaneous or subcutaneous sites. The incidence of lymphomas was similar in the groups but they appeared earlier in the beige. After 500 days 33 +/bg and 27 bg/bg mice were still alive, 60 of 83 +/bg animals (72%) and 47 of the 64 bg/bg (74%) having developed tumors. The beige group showed a higher incidence of non-thymic lymphomas, but the incidence of thymic lymphomas, cutaneous epithelial tumors and bile duct adenomas was similar in the two groups. In a continuing study of NK intact B10 (27), B10A (25), B10.BR (39), B10G (48) mice and NK cell deficient B10S congenic animals (30), squamous carcinomas have developed more frequently in B10S animals (B10S 8/30-27%) rest (1/139-8%, P less than 0.01). At present it looks as though both thymic and extra thymic lymphomas may also be of increased frequency in the B10S, NK deficient animals. The role of DMBA as a suppressor has been confirmed. (no Refs)

36. TUMOR SUSCEPTIBILITY IN TWO MOUSE STRAINS WITH VARYING DOSES OF CARCINOGEN.

Bernfeld P, Homburger F
Bio Res. Inst., Cambridge, MA, 02141
Proc Soc Exp Biol Med; 170(1):39-41 1982

Previous work by other authors reported a reverse in rank order of tumor susceptibility of 10 mouse strains when the carcinogen dose was drastically reversed. The present authors attempted to repeat this finding by following tumor formation in C3H/HJ and C57BL/6J mice after sc administration of 5, 25, 125, and 625 ug of 3-methylcholanthrene (MC). In the previous study carcinogen administration was by imbedded paraffin disk. Because this disk could not be found in some cases, 2-50% of the mice were removed from the experimental groups, all without tumor formation. In this study a fair to good dose-response relationship was obtained at all four dosage levels, with C57BL/6J mice showing the higher susceptibility. The differences between strains were not significant by the Chi square test. Plotting data by another method used by the previous authors gave the same results. The authors feel that the previously reported reversal of tumor susceptibility with low carcinogen dose was due to the skewing of results when the animals with missing paraffin disks were removed from experimental consideration. (3 Refs)

37. INDUCTION OF MAMMARY TUMORS IN VIRGIN FEMALE BALB/C MICE BY SINGLE LOW DOSES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:905 1982

These experiments were initiated to examine the relationship between low doses of DMBA and the induction of mammary tumors in virgin female BALB/c mice. Twelve-week-old mice were exposed to single or multiple doses of DMBA ranging from 0.0025 mg to 12.0 mg by gastric intubation. Mice were checked regularly for mammary tumors and the experiment was terminated when the mice were 800 days of age. In the dose range of 0.0025 mg to 0.125 mg of DMBA the incidence of mammary tumors was directly proportional to dose. At doses above 0.125 mg the dose response curve began to bend over and above 0.5 mg the mammary tumor incidence was independent of dose. In the low dose region administration of DMBA as multiple exposures did not affect the tumor response. Analysis of the data for the incidence of mammary tumors with time after DMBA administration suggested that carcinogen exposure both accelerated the appearance of otherwise 'spontaneous' neoplasms as well as induced new mammary tumors. Further, the predominant effect of increasing the dose of DMBA was to shorten the time of onset of these tumors without changing their rate of appearance. Finally, carcinogen dose affected the histological type of tumors observed. Greater than 90% of the mammary tumors induced by DMBA doses which were on the ascending portion of the dose response curve were adenocarcinomas. At doses which were on the plateau of the dose response curve, increasing the dose served only to increase the relative proportion of adenoacanthomas to adenocarcinomas. (no Refs)

38. HIGH SKIN TUMOUR INITIATING ACTIVITY OF THE METABOLICALLY DERIVED TRANS-3,4-DIHYDRO-3,4-DIOL OF THE CARCINOGEN 15,16-DIHYDRO-11-METHYLCYCLOPENTA[A]PHENANTHREN-17-ONE.

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Carcinogenesis; 3(4):449-451 1982

Eight main metabolites of the parent carcinogen 15,16-dihydro-11-methylcyclopenta[a]phenanthrene-17-one (1) were assayed for their ability to initiate skin tumors in TO mice after topical application in two-stage experiments with croton oil used as the promoter. All were less active than 1 with the exception of the trans-3,4-dihydro-3,4-diol which was more than 10x as active. This diol is therefore confirmed as the proximate carcinogen, a conclusion reached previously on different evidence. (Author abstract) (13 Refs)

39. INDUCTION OF HYPERPLASTIC LIVER NODULES IN HEPATECTOMIZED RATS TREATED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE, BENZO[A]PYRENE OR PHENOBARBITAL BEFORE OR AFTER EXPOSURE TO N-2-FLUORENYLACETAMIDE.

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First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 73(2):264-269 1982

The effects of pre- and post-administration of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), benzo[a]pyrene (B[a]P), and phenobarbital (PB) on the induction of hyperplastic liver nodules by N-2-fluorerylacetamide (2-FAA) were studied in F344 rats. Rats were given 3'-Me-DAB (0.06% in the diet), B[a]P (80 mg/kg b wt x 7, intragastrically) or PB (0.05% in the diet) for 6 wk before (experimental series I) or after (experimental series II) diet containing 0.02% 2-FAA for 2 wk, and killed in wk 10 of the experiment. The number and total area of hyperplastic nodules per unit area of liver were greatest in rats treated with 3'-Me-DAB in both experimental series. B[a]P significantly increased the induction of hyperplastic nodules in experimental series I and PB significantly increased it in experimental series II. Partial hepatectomy performed during administration of test chemicals enhanced the induction of hyperplastic nodules, especially in experimental series I, and an oral dose of carbon tetrachloride during 2-FAA feeding enhanced it in both experimental series. In the present system, initiating activity of both the hepato- and the non-hepatocarcinogen was detected, and promoting activity of both the hepatocarcinogen and the hepatopromoter was demonstrated. (Author abstract) (23 Refs)

40. QUANTIFICATION OF THE CARCINOGENIC EFFECT OF POLYCYCLIC AROMATIC HYDROCARBONS IN USED ENGINE OIL BY TOPICAL APPLICATION ONTO THE SKIN OF MICE.

Grimmer G, Dettbarn G, Misfeld J, Brune H, Deutsch-Wenzel R
Biochemical Inst. Environmental Carcinogenesis, Sicker Landstrasse 19, D-2070 Ahrensburg, W. Germany
Int Arch Occup Environ Health; 50(1):95-100 1982

The carcinogenic effects of used motor oil and its constituent fractions were compared in female SPF mice. Animals bearing local tumors after application of test substances (from low to high doses) to the skin were tested for the carcinogenic impact. The following results were obtained: 4.6-69.4% for used lubricating oil, 1.5-3% for polycyclic aromatic hydrocarbons (PAH) free fraction, 6.2-9.2% for PAH-containing fraction (hydrocarbons with two and three rings), 0-53.2% for PAH-containing fraction (hydrocarbons with more than three rings), 4.9-53.9% for reconstituted oil from all fractions, 40.0-93.8% for benzo(a)pyrene, 1.5% for solvent, 0% for untreated animals. The PAH fraction containing PAH with more than three rings was by far the most potent fraction, provoking 20 benign and 13 malignant local tumors in the highest dose of 0.0619 mg/mouse. The carcinogenic effect of this PAH fraction was similar to that of reconstituted oil but not to that of the original oil sample, indicating that lower mol wt PAH may have been volatilized during fractionation procedures. (11 Refs)

41. THE CARCINOGENESIS OF B LYMPHOCYTES IN PEYER'S PATCHES OF RATS (MEETING ABSTRACT)

Bost KL, Cuchens MA
Department of Microbiology, University of Mississippi Medical Center, Jackson, MS, 39216
Fed Proc; 41(3):553 1982

Spontaneously arising B cell leukemias in experimental animals are rare. Furthermore the experimental protocols used to induce lymphoid malignancies seemingly have little efficacy in the induction of malignancies of B cell origins. Therefore a different approach was used in the study reported here. The basic procedure was to localize a chemical carcinogen in the Peyer's patches of rats which were previously treated with anti-IgD to induce B cell proliferation in vivo. Thus far 9 of 15 3-methylcholanthrene (MCA) and 4 of 14 7,12-dimethylbenzanthracene (DMBA) treated rats have developed lymphoid malignancies which have been characterized, based on morphology, growth kinetics, pathogenesis and cell surface markers, as: 1) B cell chronic lymphocytic leukemias which coexpress membrane IgM and IgD (3 MCA treated rats), 2) Immature B cell leukemias which preferentially express membrane and/or cytoplasmic IgM (3 MCA treated rats), 3) B cell nodular lymphomas with immunoblastic characteristics (3 MCA and 1 DMBA treated rats) and 4) T cell thymomas (3 DMBA treated rats). Studies have also been done to propagate the B cell malignancies in vivo and in vitro. These studies indicate that the treatment of Peyer's patches with chemical carcinogens may provide a selective means of inducing B lymphocytic malignancies. (no Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

42. CHEMICAL CARCINOGEN (HYDRAZINE, POLYNUCLEAR HYDROCARBON AND/OR SYNTHETIC JET FUEL COMPONENTS) INDUCED CARCINOGENESIS OF HUMAN CELLS, IN VITRO.

Milo GE
Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH
Chemical Carcinogen (Hydrazine, Polynuclear Hydrocarbon and/or Synthetic Jet Fuel Components) Induced Carcinogenesis of Human Cells, In Vitro. Available from National Technical Information Service, Springfield, VA, as AD-A107 721/3:, 127 pp., 1981.

Select chemicals of interest to the Air Force and identified as man made environmental contaminants have been found to neoplastically transform human cells in vitro. Benzo(a)pyrene one of these compounds of interest, exhibits unique features of movement from the extracellular environment to the nucleus of the cell. B(a)P is transported into human foreskin fibroblasts from the plasma membrane to the nucleus by binding as the unmetabolized parent B(a)P. B(a)P forms a low binding association with a lipoprotein complex in the cytoplasm that has a mol wt of 12,500. The B(a)P following penetration into the nucleus is then oxygenated to various metabolites. Benzopyrene-diol-epoxide-1 has been identified as a metabolite in the nucleus that interacts with deoxy-guanine to form a DNA adduct, 7R-BPDE-I-dG. We then used another hydrocarbon 1,2,3,4-tetrahydro-7,12-dimethyl benz(a)anthracene to induce carcinogenesis in human cells. To date we have no evidence for extracellular or intracellular metabolism of this compound under conditions for transformation. We conclude tentatively that this data

suggests that there is an alternate requirement for polynuclear hydrocarbon induced carcinogenesis in human cells compared to rodent cells. (Author abstract)

43. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT- AND INDIRECT-ACTING CARCINOGENS.

Nesnow S, Garland H, Curtis C
Genetic Toxicology Div., Health Effects Res. Lab., United States Environmental Protection Agency, Research Triangle Park, NC, 27711
Carcinogenesis; 3(4):377-380 1982

Oncogenic transformation of C3H10T1/2CL8 cells was improved by treating the cells 5 days after seeding. Benzo[a]pyrene-induced transformation was increased 3.5-fold by this method, compared with treating the cells 1 day after seeding. N-Methyl-N'-nitro-N-nitrosoguanidine, which does not transform asynchronous cultures of C3H10T1/2CL8 cells when administered 1 day after seeding, produced an average of one focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and aflatoxin B1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined clonal cytotoxicity was reduced when they were administered 5 days after seeding. These results indicate the utility of this new procedure for the qualitative analysis of the transforming ability of chemicals. (Author abstract) (28 Refs)

44. EFFECT OF DIETARY PROTEIN ON INDUCTION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE MUTAGENESIS BY RAT LIVER MICROSOMES IN THE SALMONELLA/MICROSOME TEST SYSTEM (MEETING ABSTRACT)

Singletary KW, Martin SE, Milner JA
Department of Food Science, University of Illinois, Urbana, IL, 61801
Fed Proc; 41(3):356 1982

Studies have shown that a high protein diet decreases the incidence of 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors in rats. The present studies were designed to evaluate the influence of dietary protein on the ability of rat liver microsomes to mediate DMBA-induced mutagenesis. Female rats (150g) were fed isocaloric diets containing 7.5, 15.0 or 45.0% protein as casein for 2 weeks. All rats were treated with Aroclor (100mg/kg) 5 days before sacrifice. Liver homogenates (S-9) were prepared and evaluated for their influence on the mutagenicity of DMBA (20 g/plate) with Salmonella typhimurium TA98. S-9 fractions from rats fed the 7.5% protein diet produced approximately 100% more DMBA-induced revertants per mg protein than S-9 fractions from rats fed the 15 or 45% protein diets. Pair feeding studies revealed food intake did not account for these differences. The duration of feeding was also found to influence the S-9 activation effects of dietary protein. These results suggest that the Salmonella/microsome mutagenesis assay has potential use as a relatively simple and rapid system to evaluate the influence of dietary protein source and concentration as factors modifying carcinogenesis. (no Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

45. CONFORMATION CHANGE OF DNA INDUCED BY 6-OXYBENZO[A]PYRENE RADICAL.

Sato Y, Okano T
Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gann; 73(2):309-314 1982

The interaction of 6-oxybenzo[a]pyrene radical with DNA with 50% methanol solution was studied in order to determine whether the radical molecule influences DNA conformation. The mode of the interaction of 6-oxybenzo[a]pyrene radical with DNA differed from that of other benzo[a]pyrene derivatives such as 6-hydroxybenzo[a]pyrene, diol-epoxides, etc. The physical binding of the radical molecule to DNA seemed to be transient. This physical binding is most likely due to adsorption at the external surface of DNA, i.e., simply contact in character. It is likely that the local base-pairs are tilted by the contact due to hydrophobic interactions. Furthermore, it is concluded that the covalently bound radical molecule, which is mainly introduced on guanine base, induces a twist of the base plane with respect to other base planes. (Author abstract) (34 Refs)

46. REACTIVITY OF DIBENZOPYRENES IN UV- AND GAMMA-RADIATION INITIATED OXIDATION REACTIONS

Paalme L, Ulboprus K, Peiapill J, Goubergrits M, Bahna L, Jacquignon PC
Inst. Chemistry, Acad. Sciences of Estonian SSR, Tallina, USSR
Neoplasma; 29(1):29-35 1982

The kinetics of UV- and gamma-irradiation-initiated oxidative degradation of dibenzopyrenes (diBP) was studied, its rate constants in benzene and/or n-octane solutions were determined and an attempt was made to compare the kinetics data with the electronic energies of singlet and triplet excited states and with the values of half-wave potentials of polarographic reduction. Some essential products of oxidation (quinones) were identified by using thin-layer chromatography and spectrophotometry. (Author abstract) (10 Refs)

47. EFFECTS OF CARCINOGENS ON THE PARTITION OF CELLS IN AQUEOUS POLYMERIC TWO-PHASE SYSTEMS.

Andreeva EA, Belisheva NK, Freedlanskaya II, Pinaev GP, Blomquist G
(c/o Blomquist) Dept. Occupational Health, Natl. Board Occupational Safety and Health, Box 6104, S-900 06 Umea, Sweden
Chemosphere; 11(4):377-381 1982

A two-phase system composed of Dextran 500 and polyethylene glycol was used to separate cancerous from normal rat fibroblasts, rat hepatocytes, mouse hepatocytes, and mouse fibroblasts. Treatment of normal cells with the carcinogens 7,12-dimethylbenzanthracene and dibenz(a,h)anthracene changed the cell partitioning behavior toward that of cancer cells, but treatment of normal cells with the noncarcinogen phenanthrene changed the membrane properties in the opposite way. (14 Refs)

REVIEWS AND OTHER RELATED STUDIES

48. METABOLISM OF CHEMICAL CARCINOGENS.

Weisburger JH, Williams G
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York Plenum Press, 714 pp., 1982.

Chemical carcinogens are defined by their ability to induce tumors, four types of response have generally been accepted as evidence of tumorigenicity. These include an increased incidence of the tumor types occurring in controls, the occurrence of tumors earlier than in controls, the development of types of tumors not seen in controls, and an increased multiplicity of tumors in individual animals. Examples of the genotoxic carcinogen class include alkylating agents which are activation independent, aromatic amines and polycyclic aromatic hydrocarbons which are activation-dependent, and metals. Examples of the epigenetic carcinogen class include plastics and asbestos, estrogen, androgen, purine analog, and phorbol ester. Promotors are agents that increase the tumorigenic response to a carcinogen when applied after the carcinogen. Genetic factors, sex and endocrine status, age, diet, activities of intestinal flora, the presence of other chemicals, the mode and frequency of exposure, and numerous other factors influence the variation in carcinogen metabolism. Research during the last few decades has pinpointed natural products as major causes of cancer in humans in various parts of the world. (486 Refs)

49. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York Plenum Press, 714 pp., 1982.

The nature of modified nucleic acids following interactions with carcinogens is reviewed. Interactions of chemical carcinogens with DNA include covalent interactions such as alkylating agents, nitrosamines and nitrosamides, and noncovalent interactions of both internal and external binding types. Purine-N-oxides and many inorganic metal compounds are known to be carcinogenic. The use of fractionation techniques has revealed that carcinogens exhibit a preferential interaction with some regions of DNA in euchromatin. Interactions of chemical carcinogens with RNA have been studied, and alterations in RNA have been attributed to alkylating agents such as nitrosamines and nitrosamides, to arsenan, to aromatic amines and amides, and to polycyclic aromatic hydrocarbons. Interactions of carcinogens with nucleic acids exert a profound effect on the structure and synthesis of DNA and RNA, gene expression, and regulation of cellular development. Although the exact mechanism or mechanisms by which DNA damage and repair are involved in carcinogenesis is not completely understood, there is overwhelming evidence indicating a causal relationship between these two processes. (634 Refs)

50. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT

Nettesheim P, Topping DC, Jamasbi R
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709

Annu Rev Pharmacol Toxicol; 21:133-163 1981

Selected laboratory studies conducted during the last decade that exemplify what has been learned about the multicomponent etiology of lung cancer are reviewed. Sections concerning experiments relating to modification of host susceptibility include the following: studies on age specific susceptibility of respiratory tract epithelium to carcinogens, effect of immune suppression on the development of respiratory tract tumors, role of dietary vitamin A in the susceptibility to lung cancer induction, and role of respiratory tract infections in the pathogenesis of lung cancer. Sections concerning the interaction of environmental or occupational agents include: two stage carcinogenesis in respiratory tract epithelium, cocarcinogenic effects of chrysotile asbestos, role of so-called inert particles in respiratory tract carcinogenesis, nickel subsulfide as a possible cocarcinogen in occupational lung cancer, studies on benzo(e)pyrene as a cocarcinogen, and role of irritant gases and vapors as cocarcinogens in the respiratory tract. (117 Refs)

51. FATE OF EPOXIDES.

Oesch F
Inst. Pharmacology, Univ. Mainz, D-6500 Mainz, W. Germany

Adv Exp Med Biol; 136(partA):9-52 1982

Structure-activity relationships for the mutagenicity of a series of closely related epoxides are described and control of reactive metabolites derived from closely related aromatic compounds by different enzymes is discussed. The mutagenicity of a homogeneous series of 17 epoxides was studied using four tester strains of Salmonella typhimurium. In strains TA 100 and TA 1535, which are base-pair substitution mutants, 12 of the epoxides were detected as mutagens. A number of structurally similar 1,2-disubstituted oxyranes, which occur as structural units in a wide variety of drugs and natural compounds, are weak or moderate mutagens. The presence of the double bond in formal conjugation with the epoxide ring increased the mutagenicity relative to the saturated oxyrane. The mutagenicity of benz[a]anthracene investigated in the mammalian enzyme mediated Salmonella test was affected very differently by the same modifications of the metabolizing system, in spite of very similar chemical structures and physicochemical properties of the compounds studied. Microsomal epoxide hydrolase activity in different species towards three different substrates is presented. Epoxides are electrophilic reactive to varying degrees and can chemically react with nucleophilic tissue constituents thereby altering critical cellular macromolecules including DNA, RNA, and proteins. Non-enzymic rearrangement and several enzyme catalyzed reactions compete with this covalent binding. (34 Refs)

52. NEOANTIGEN EXPRESSION IN CHEMICAL CARCINOGENESIS.

Baldwin RW, Price M
Cancer Res. Campaign Laboratories, Univ. Nottingham, Nottingham, England
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982

Neoantigens have been found on tumors which were chemically induced by polycyclic hydrocarbons, by aminoazo dyes, by aromatic amines, by alkylnitrosamines, and by hydrazines. Several findings are consistent with the view that tumor-associated antigens on chemically induced tumors are expressed on integral membrane proteins or glycoproteins. Attempts to develop cell-free radioimmunoassays for these antigens have generally been unsuccessful. One of the major problems has been to retain the capacity of the radiolabeled antigens to rebind with antibodies in syngeneic immune sera. The significance of the possible relationships between tumor-associated neoantigens and products of major histocompatibility complex needs to be further evaluated. Oncodevelopmental antigens appear to be associated with numerous types of chemically induced tumors, and thus they should be regarded as valuable potential markers for studying transformation-related events. Three possible pathways leading to neoantigen expression include their appearance as a consequence of early interactions of carcinogen with target cells, their expression which only occurs once the initiated cell is converted to the preneoplastic cell, and their expression at the stage when malignant cell clones develop. (328 Refs)

53. SMOKING AND CANCER.

Lapis K
No affiliation given
Magy Tud; 89(2):119-127 1982

Epidemiological and etiological relationships between smoking and cancer, especially lung caner, are discussed. The carcinogenic substances occurring in tobacco and cigarette smoke include polycyclic aromatic hydrocarbons, such as benzo(a)pyrene, N-nitrosamines, such as N-nitrosonornicotine, and 210-polonium. Increased incidence of cancer of the larynx, pharynx, lips, oral cavity, tongue, esophagus, urinary bladder, pancreas, and especially lung was observed among smokers compared with nonsmokers. (no Refs) (In HUN)

54. SMOKING AND DRUG METABOLISM.

Dawson GW, Vestal RE
Clinical Pharmacology Unit, Veterans Admin. Medical Center, Boise, ID, 83702
Pharmacol Ther; 15(2):207-221 1981

Constituents of tobacco smoke, including polycyclic aromatic hydrocarbons, nicotine, carbon monoxide, trace metals, cyanide, and pesticides, are discussed; relationships between smoking and the metabolism of selected drugs are reviewed. Some drugs, such as phenacetin, theophylline, and antipyrine, seem to be metabolized much faster in smokers than in nonsmokers. Others, such as glutethimide, exhibit altered bioavailability. Some benzodiazepines produce greater side-effects, particularly drowsiness, in nonsmokers than in smokers, and the amount of smoking is roughly correlated with decreased drowsiness. Ethanol and caffeine metabolism are also altered by smoking habits; smokers tend to drink more coffee, possibly due to higher rates of elimination of caffeine. Propranolol elimination is altered by smoking; effects on blood pressure, heart rate, and other circulatory parameters may counteract the antihypertensive value of this and related drugs. Smoking and its subsequent effects should be regarded as covariants in drug action and interaction in man. Smoking status should be considered as a variable such as age, race, sex, weight, or concurrent disease states in drug studies. (129 Refs)

55. MAJOR APPROACHES TO THE EXPERIMENTAL STUDY OF LUNG CANCER.

Pliss GB, Turusov VS, Zabezhinski MA
No affiliation given
Vopr Onkol; 28(2):18-27 1982

Experimental models used in the study of the etiology and pathogenesis of lung cancer are reviewed. The experimental lung tumors should meet following requirements: ease of induction, high selectivity and reproducibility, and similarity with human tumors with respect to the morphology and clinical manifestations. Metabolism of various carcinogens was studied in organ cultures of human brorchi. Experiments in nude mice subjected to sc implantation of the fragments of human bronchi and administration into the transplants of the pills containing 7,12-dimethylbenz(a)anthracene or 3-methylcholanthrene provided additional data on the sensitivity of bronchial epithelium to various carcinogens and the characteristic features of different stages of carcinogenesis. Experimental models confirmed the role of chronic lung diseases in the etiology of lung cancer. Experimental studies of the dose-effect curves during pulmonary carcinogenesis induced by polycyclic hydrocarbons provided the basis for the estimation of the maximum permissible levels of benzo(a)pyrene in the air. (20 Refs) (In RUS)

56. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.

Bentashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982

Incidence of spontaneous and induced tumors of the peripheral nervous system (PNS) in the experimental animals is reviewed. PNS neoplasms were induced after sc or im applications of polycyclic hydrocarbons. Injection of methylcholanthrene into the sciatic nerve produced tumors in rabbits and in random-bred rats. The spectrum of nitrosamine-induced PNS tumors was shown to depend upon the animal species, age, strain, dose, and the mode of administration. Prolonged iv administration of methylnitrosourea (MNU) resulted in selective induction of CNS and PNS tumors. High incidence of neurogenic tumors was recorded in Fisher and BD-IX rats. Ethylnitrosourea (ENU) showed high affinity to PNS during transplacental carcinogenesis. Sensitivity of rat embryo to ENU was 30-50x greater than that of the adult rats. The highest incidence of PNS tumors was observed after ENU administration during the last third of the gestation. Nitroso compounds and urethane were reported to induce tumors of the sympathetic nervous system in rabbits, hamsters, and rats. (103 Refs) (In RUS)

57. ETIOLOGY OF MOUTH AND LIP TUMORS.

Zabezhinski MA, Godorozha PD
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 28(2):105-113 1982

Literature data on the etiology of mouth and lip cancers are reviewed. Pathogenesis of mouth neoplasms is associated with the exposure to various chemical, physical, and biological car-

cinogenic factors alone or in combination with the modifying factors. The increased incidence of mouth cancer can be caused by smoking, tobacco chewing, exposure to polycyclic aromatic hydrocarbons, alcohol consumption, and exposure to pesticides. Physical carcinogens include UV, x rays, and sunlight. Experimental data indicate that herpes virus and polyoma virus can induce adenomas and adenocarcinomas of mouth mucosa. Poor hygiene of the mouth can increase the risk of development of mouth cancer. Chronic irritation of the mouth mucosa was shown to enhance penetration of carcinogens into mucosa and to stimulate cell proliferation. Bacterial flora of the oral cavity was shown to contribute to the metabolism of chemical carcinogens. Deficiency of vitamins A and B led to development of precancerous conditions of the mouth mucosa. (74 Refs) (In RUS)

58. MUTAGENS IN HEATED FOODS.

Pariza MW
Food Res. Inst., Dept. Food Microbiology and Toxicology, Univ. Wisconsin, Madison, WI, 53706
Food Technol; 36(3):53-56 1982

Mutagens in heat-processed foods are discussed with respect to effects of time and temperature on mutagen formation, chemical inhibition of mutagenesis and carcinogenesis, and safety considerations. Formation of carcinogenic polycyclic aromatic hydrocarbons and tryptophan on broiled meats is dependent on relatively high temperature; however, mutagenic activity recently has been found in a variety of foods processed under more moderate conditions. Temperature/time evaluations in ground beef during frying have demonstrated that mutagen formation is temperature dependent: Mutagenic activity readily developed at frying temperatures of 191 C or 210 C, whereas only low levels of mutagenic activity was observed at all time intervals during frying at 149 C. A number of chemicals, including beta-naphthoflavone, butylated hydroxytoluene, butylated hydroxyanisole, and polycyclic aromatic hydrocarbons, inhibit cancer in animals when fed before or during carcinogen administration, apparently via enzyme induction. Epidemiologic studies indicate a correlation between increased cancer incidence at some sites and diets high in charred and/or heavily smoked foods. Experimental evidence, however, does not suggest that mutagens in the diet play an important role in this correlation. (26 Refs)

59. PREDICTIVE IDENTIFICATION OF HYPERSUSCEPTIBLE INDIVIDUALS.

Omenn GS
Dept. Environmental Health, Univ. Washington, Seattle, WA, 98195
JOM; 24(5):369-374 1982

Genetic traits that may predispose individuals to occupational diseases are reviewed. A single-gene difference affecting N-acetyl-transferase (NAT) activity in liver makes individuals slow acetylators (recessive) or rapid acetylators (dominant) of a series clinically important drugs. NAT is known to be involved in acetylation and thus inactivation arylamines that are potent bladder carcinogens, including beta-naphthylamine, benzidine, 4-amino-biphenyl, and 4-nitrobiphenyl, all of which are used as industrial oxidants. An excess of slow acetylators has been observed in groups with a high incidence of occupational bladder cancers. Genetic control of microsomal oxidizing systems appears to be related to certain occupational disease. Aryl hydrocarbon hydroxylase (AHH) has been shown to be involved in activating many promutagenic and procarcinogenic aryl hydrocarbons, of which benzopyrene is the prototype. The pesticide parathion and its active metabolite paraoxon are inactivated by plasma paraoxonase. Potential genetic predispositions due to differences in tissue sensitivity include the following: hemolysis due to glucose 6-phosphodieterase; sickle cell trait; plasma alpha-antitrypsin deficiency and pulmonary emphysema; low-back pain, ankylosing spondylitis, and histocompatibility antigen B27; and skin hypersensitivity reactions. Opportunities for research criteria for development of screening tests are discussed. (35 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of Carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye C
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

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Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
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CHEMICAL CARCINOGENESIS

Polycyclic Aromatic Hydrocarbons and Related Compounds

SERIES CK07 No. 82/11 NOVEMBER, 1982

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. DETECTION OF POLYCYCLIC AROMATIC HYDROCARBONS IN SKIN OIL OBTAINED FROM ROOFING WORKERS.

Wolff MS, Tafte B, Boesch RR, Selikoff IJ
Div. Environmental Medicine, Mount Sinai Sch. Medicine, New York, NY, 10029

Chemosphere; 11(6):585-590 1982

Blood serum and skin oil samples from roofing workers were analyzed for polycyclic aromatic hydrocarbons (PAH) to assess tissues burdens of PAH. In six serum samples, PAH were below the limit of detection (1-60 picog/ml). However, in skin oil of nine roofers, PAH were detected at 0.02-13 ug/g (lipid wt of skin oil), or a total of 0.048-36 nanog/36 square cm

HE 20.3173/2:

in a half period. The presence of PAH in skin oil provided evidence of continued body burden of these chemicals after leaving the workplace. Elimination by metabolism provides the obvious opportunity for dermal, as well as systemic, insult of metabolites of PAH, which are known to possess powerful carcinogenic activity. (13 Refs)

2. HEALTH EFFECTS RESEARCH IN DIRECT COAL LIQUEFACTION. STUDIES OF H-COAL DISTILLATES: PHASE I. PDU SAMPLES - THE EFFECTS OF HYDROTREATMENT.

Epler JL, Fry RJ, Larimer FW
Oak Ridge Natl. Lab., Oak Ridge, TN
Health Effects Research in Direct Coal Liquefaction. Studies of H-Coal Distillates: Phase I. PDU Samples - the Effects of Hydrotreatment. Available from National Technical Information Service, Springfield, VA, as DE82003702, 66 pp., 1981.

A multi-divisional effort aimed at the integrated assessment of the health and environmental effects of various coal conversion and shale oil technologies is being carried out. The feasibility of using health effects bioassays to predict the potential biohazard of various H-Coal derived test materials is examined in a coupled chemical and biological approach. The primary focus of the research is the use of preliminary chemical characterizations and preparation for bioassay, followed by testing in short-term assays in order to rapidly ascertain the potential biohazard. Mammalian toxicological assays parallel the testing. Raw and hydrotreated product liquids from process development units of H-Coal and the pilot plant solvent refined coal process were examined for acute toxicity monitored as population growth impairment of Tetrahymena exposed to aqueous extracts and for mutagenic activity monitored as revertants of Salmonella exposed to metabolically activated chemical class fractions. Medium to high severity hydrotreatment appears to be an effective means of reducing biological activity, presumably by reducing the aromaticity and heteroatom content. Five basic mammalian, acute toxicity tests have been conducted with selected H-coal samples and shale oil derivatives. The data show that H-Coal samples are moderately toxic whereas the toxicity of shale oil derived products is slight and comparable to samples obtained from naturally occurring petroleums. No overt skin or eye toxicity was found. The present data reveal that coal-derived distillates generated by the H-coal process are highly carcinogenic to mouse skin. An extreme form of neurotoxicity associated with dermal exposure to one of the lighter, minimally carcinogenic, materials was noted. (Author abstract)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

3. HETEROGENEITY IN THE RATE OF BENZO[A]PYRENE METABOLISM IN SINGLE CELLS: QUANTITATION USING FLOW CYTOMETRY.

Miller AG, Whitlock JP
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Mol Cell Biol; 2(6):629-634 1982

A flow cytometric method was used to quantitate heterogeneity in overall benzo(a)pyrene (BP)-metabolizing activity among the cells of a population of Hepa-1c1c7 mouse hepatoma cells, and to assess the heterogeneity within variant cell populations with decreased ability to metabolize BP. The activity of the BP-metabolizing enzyme system was induced by exposure of the cell to 1 nanoM 2,3,7,8-tetrachlorodibenzo-p-dioxin for either 2 hr or 18 hr. The fluorescence-activated cell sorter was used in conjunction with the BP disappearance assay to analyze BP metabolism at the cellular level and to isolate both high- and low-activity variants in BP metabolism. The present method is much more rapid than subcloning and generates a more representative result, since many more cells may be studied. The individuals of a cloned population exhibited heterogeneity in metabolism of BP. Low-activity variants also exhibited a propensity to become heterogeneous in BP metabolism, an inherent property and not resulting from accumulation of new variants. Heterogeneity developed rapidly and in the absence of any mutational stress. (25 Refs)

4. SEPARATION AND IDENTIFICATION OF BENZO(A)PYRENE METABOLITES FROM EXCRETION PRODUCTS.

Vasatu A, Stafidov N, Voiculet N
Inst. Oncology, Blvd. 1 Mai, no. 11, Bucharest 78159, Romania
Rev Roum Biochim; 18(4):303-311 1981

After po loading of Wistar rats with benzo(a)pyrene (BP; 60 mg/day x 3), urine was collected for 5 days (starting 24 hr after first administration). Analyses of urine showed that 65-75% of the BP was eliminated in the first 24 hr, 9% of which was unchanged. Three groups of BP-hydroxylated derivatives (diols, quinones and phenols) were found in variable proportions depending on time of collection. Higher amounts of diols and quinones were found in the 24 hr collection while large amounts of phenols were found in the 96 and 120 hr urine samples. (16 Refs)

5. METABOLIC ACTIVATION OF BENZO(A)PYRENE BY TRANSFORMABLE AND NONTRANSFORMABLE C3H MOUSE FIBROBLASTS IN CULTURE.

Gehly EB, Heidelberger C
c/o Heidelberger Cancer Res. Lab., Univ. Southern California, Comprehensive Cancer Center, Los Angeles, CA, 90033
Cancer Res; 42(7):2697-2704 1982

Incubation of 2.5 uM benzo(a)pyrene (BaP) with C3H/10T1/2 or CVP3SC6 (CVP) mouse fibroblasts for 48 hr resulted in the metabolism of 36 to 42% of the BaP to organic soluble derivatives, which cochromatographed with 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene, 9,10-trans-dihydroxy-9,10-dihydrobenzo(a)-pyrene, 3-hydroxybenzo(a)pyrene, and 9-hydroxybenzo(a)pyrene, or to water-soluble derivatives. The formation of both organic and water-soluble metabolites during the 48-hr period increased proportionally with time, except in the case of BaP phenols, which increased initially but then remained the same or decreased. The distribution of organic soluble metabolites in the extracellular culture medium consisted primarily of BaP diols and was significantly different from that found inside the cells. The intracellular profile of organic soluble metabolites produced by both cell lines consisted predominantly of BaP phenolic derivatives and was qualitatively similar to the spectrum of metabolites produced by the incubation of BaP with C3H/10T1/2 or CVP cell microsomes. The nature of the BaP water-soluble derivatives produced by the C3H/10T1/2 and CVP cell lines was investigated by hydrolysis of culture medium with beta-glucuronidase and arylsulfatase. Although sulfation was not a major conjugation pathway for BaP in these cells, glucuronidation of BaP phenols was found to account for 30% of the total water-soluble deriva-

tives. The similarity in the kinetics and qualitative nature of the metabolism of BaP by C3H/10T1/2 and CVP cells indicates that both cell lines are equally capable of biosynthesizing the proximal carcinogen, 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene. Analysis of the water-soluble metabolites produced by these cells suggests further that the nonresponsiveness of the CVP cells to BaP-induced transformation cannot be accounted for on the basis of an increased detoxication of 7,8-trans-dihydroxy-7,8-dihydrobenzo(a)pyrene. (Author abstract) (34 Refs)

6. METABOLISM OF BENZO(A)PYRENE BY HUMAN EPITHELIAL AND FIBROBLASTIC CELLS: METABOLITE PATTERNS AND DNA ADDUCT FORMATION.

Bartley J, Bartholomew JC, Stampfer MR
Peralta Cancer Res. Inst., Peralta Hosp., Oakland, CA
J Cell Biochem; 18(2):135-148 1982

The metabolism of benzo(a)pyrene (BaP) and DNA adduct formation were compared in the same incubations of mammary epithelial cells grown out in early passage, from each of three human subjects, and of fibroblasts from one of these subjects. Mammary epithelial cells showed the preferential formation of 7,8-dihydrodiol-9,10-dihydroepoxybenzo(a)pyrene, (BPDE) the ultimate carcinogen. The end products of BaP metabolism in fibroblasts, unlike epithelial cells, were mainly mono- and dihydroxide derivatives of BaP. The greater ease of DNA adduct formation in epithelial cells is apparently related to the metabolites produced from BaP by these cells. The metabolite results indicate that mammary epithelial cells preferably converted BaP to diols, some of which were conjugated with glutathione at the first epoxidation step. The remaining dihydrodiols were readily converted to BPDE, a large portion of which ended up as tetrols and glutathione conjugates, but in the process BPDE was available to react with DNA. The accumulation of diols in the later stages of fibroblast incubations indicates that these cells have a much lower capacity to convert diols to the diolepoxide than do mammary epithelial cells. These results support the theory that chemical carcinogens may be involved in the induction of human breast cancer. (46 Refs)

7. BENZO(A)PYRENE METABOLISM IN PRIMARY CULTURES OF MOUSE EPIDERMAL CELLS AND UNTRANSFORMED AND TRANSFORMED EPIDERMAL CELL LINES.

DiGiovanni J, Miller DR, Singer JM, Viaje A, Slaga TJ
Wistar Inst., Philadelphia, PA, 19104
Cancer Res; 42(7):2579-2586 1982

The metabolism of [3H]benzo(a)pyrene [B(a)P] by cultures of primary mouse epidermal cells and untransformed and transformed epidermal cell lines was investigated. All three cell types effectively metabolized [3H]B(a)P. The major organic solvent-extractable metabolites found intracellularly in primary cultures were trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene and 3-hydroxybenzo(a)pyrene although quantities of 9-hydroxybenzo(a)pyrene, trans-9,10-dihydro-9,10-dihydroxybenzo(a)pyrene, and quinones also were present. The major organic solvent-soluble metabolites found in the extracellular medium were trans-9,10-dihydro-9,10-dihydroxybenzo(a)pyrene and trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, with smaller quantities of unconjugated phenols and quinones. The major water-soluble metabolites found in the extracellular medium were conjugated with glucuronic acid [primarily 3-hydroxybenzo(a)pyrene and several quinones]. No sulfate conjugates of [3H]B(a)P metabolites were detected. [3H]B(a)P metabolism was similar in cultures of untransformed and transformed epidermal cell lines but differed from the primary cultures. The major intracellular and extracellular organic solvent-soluble metabolites were diols. Little or no unconjugated phenols were detected. Both the untransformed and transformed epidermal cell lines converted [3H]B(a)P to water-soluble metabolites, primarily glucuronide conjugates. In contrast to the primary cells, a major pathway of trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene metabolism in the untransformed and transformed cell lines was to a glucuronide conjugate. Primary mouse epidermal cells provide an important model system for studying factors affecting the activation and detoxification of hydrocarbon carcinogens. (Author abstract) (54 Refs)

8. ORGANOTROPIC DIFFERINCES IN METABOLISM AND DNA BINDING OF 7,12-DIMETHYLBENZ(A)ANTHRACENE IN HUMAN FETAL CELLS (MEETING ABSTRACT).

Oravec CT, D'Ambrosio SM
Department of Radiology and Pharmacology, College of Medicine, The Ohio State University, Columbus, OH, 43210
In Vitro; 18(3,part2):288 1982

DMBA (7,12-Dimethylbenz(a)anthracene) is a potent polycyclic aromatic hydrocarbon carcinogen, both transplacentally and in the adult, when activated to an electrophilic form. The rate of metabolism and DNA binding capacity of DMBA was compared to in vitro in cells derived from human fetal brain, dermis, kidney, liver, intestine and lung. Intestinal cells metabolized approximately 30%, while the other cells tested (brain, liver, dermal, lung and kidney) metabolized 2.5-10% of the DMBA during a 48 h period. Using HPLC (high performance liquid chromatography), qualitative as well as quantitative differences in the metabolite profiles were observed in each cell culture. The level of DMBA binding to cellular DNA was of the order: intestine greater than lung greater than liver greater than dermal greater than kidney. This order parallels the metabolic rate except that kidney was much lower than expected. These studies show that DNA binding and total metabolism is different in cells from different human fetal organs. (no Refs)

9. S-ADENOSYL-L-METHIONINE IS A CARBON DONOR IN THE CONVERSION OF BENZO(A)PYRENE TO 6-HYDROXYMETHYLBENZO(A)PYRENE BY RAT LIVER S-9.

Flesher JW, Stanaburg KH, Sydnor KL
Dept. Pharmacology, Univ. Kentucky Coll. Medicine, Lexington, KY, 40536
Cancer Lett; 14(1):9-14 1982

It is reported that S-adenosylmethionine (SAM) can act as methyl donor in the metabolic conversion of benzo(a)pyrene (BP) to 6-hydroxymethylbenzo(a)pyrene (6-OH CH3-BP) by rat liver S9 fraction. NADPH, MgCl2 and synthetic 6-OH-CH3 BP and 6-methylbenzo(a)pyrene were added to a reaction mixture containing [methyl-H3]-SAM, BP and rat liver S9. High pressure liquid chromatographic analysis of reaction products indicated that either 6-methylbenzo(a)pyrene was not formed, or if formed, was rapidly converted to 6-OH-CH3-BP, the principle radiolabeled metabolite. Whether this meso-hydroxylalkyl metabolite undergoes further bay region ring oxidation or is converted into a reactive ester of the hydroxymethyl metabolite to form an ultimate carcinogen remains to be seen. (14 Refs)

10. METABOLIC ACTIVATION OF BENZO[A]PYRENE, AFLATOXIN B1, AND DIMETHYLNITROSAMINE BY A HUMAN HEPATOMA CELL LINE.

Huh N, Nemoto N, Utakoji T
Institut fur Zellbiologie (Tumorforschung),, Universitat Essen (GH), Hufelandstrasse 55, 4300 Essen 1, W. Germany
Mutat Res, 94(2):339-348 1982

The frequency of sister-chromatid exchanges (SCE) was measured in normal human fibroblasts (TIG-II) co-cultivated with human hepatoma huH-1 cells to assess the genotoxic effect of activated chemicals aflatoxin B1 (AFB), benzo[a]pyrene (B[a]P), N,N-dimethylnitrosamine (DMN), and 1,2-benzanthracene. When huH-1 cells were treated with 13 uM BA for 24 hr, aryl hydrocarbon hydroxylase activity was induced to 920 picomoles/mg protein/hr, which was approx 24x higher than the basal level. SCE frequency in TIG-II cells changed depending on the inoculum ratio of huH-1 cell to TIG-II cells in the co-culture containing 5 uM AFB. When the inoculum size of huH-1 cells was half that of TIG-II cells, the SCE frequency in TIG-II cells was markedly enhanced over the control level that remained in plateau even in the cultures with larger inocula of huH-1 cells. In the co-culture, the SCE frequency was increased depending on the dose of B(a)P: 0.1 and 12.5 uM of B(a)P induced 7.2 and 10.7 SCE/metaphase, respectively. In the cultures of TIG-II cells only, 0.5 uM of B(a)P showed no significant increase of SCE. While 2.5 and 12.5 uM of B(a)P slightly elevated the SCE frequency over the control level. Treatment with DMN increased the incidence of SCE far more efficiently in the co-cultivation than in cultures of TIG-II cells only. The SCE frequency induced by 0.4 milliM (mM) of DMN in the cultures with huH-1 cells was comparable with that induced by 10 mM of DMN without huH-1 cells. (41 Refs)

11. PROSTAGLANDIN ENDOPEROXIDE SYNTHETASE-DEPENDENT COOXIDATION OF (+-)-TRANS-7,8-DIHYDROXY-7,8-DIHYDROBENZO(A)PYRENE IN C3H/10T1/2 CLONE 8 CELLS.

Boyd JA, Barrett JC, Eling TE
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Cancer Res; 42(7):2628-2632 1982

The proximate form of the carcinogen benzo(a)pyrene, (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene (BP-7,8-diol), is cooxidized during the oxidation of arachidonic acid to prostaglandins by prostaglandin endoperoxide synthetase (PES). This enzyme can oxidize BP-7,8-diol to the reactive intermediate (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene, which binds covalently to macromolecules, is mutagenic in bacterial test systems, and forms 7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BP tetrol) isomers. We have examined the cooxidation of BP-7,8-diol in an intact cell culture system of C3H/10T1/2 clone 8 mouse embryo fibroblasts, in which both the mixed-function oxidase and PES systems are present. When BP-7,8-diol is incubated for 72 hr with approx 10(6) confluent cells, high-performance liquid chromatography analysis of the organic extractable products reveals all four pairs of BP-tetrols, with those from (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene predominating. The addition of arachidonic acid (100 uM) produced a two- to three-fold increase in the formation of BP tetrols from (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene, while the metabolism to BP-tetrols from (+-)-7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10-tetrahydrobenzo(a) pyrene was unchanged. The addition of the PES inhibitor indomethacin (100 uM) completely eliminated this stimulation. Cell transformation assays were carried out under the same conditions. The addition of arachidonic acid resulted in a 10-fold increase in foci formation, while indomethacin inhibited the increase in foci formation by 70%. These results suggest that cooxidation of BP-7,8-diol to reactive intermediates by PES can occur in an intact cell system if stimulated with arachidonic acid. In addition to mixed-function oxidase-dependent activation of carcinogens, the cooxidation of chemicals to reactive metabolites during prostaglandin biosynthesis may also play a role in carcinogenesis. (Author abstract) (26 Refs)

12. METABOLISM AND ACTIVATION OF BENZO[A]PYRENE AND BENZO-RING DERIVATIVES DURING PROSTAGLANDIN BIOSYNTHESIS.

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Diss Abstr Int [B], 42(11):4397-B 1982

The cooxygenation of benzo(a)pyrene (BP) and two of its benzo-ring derivatives by ram seminal vesicle preparations has been investigated. The system was first characterized using BP as the substrate. The process was shown to be peroxidatic in nature, utilizing the hydroperoxy compound PGG2 generated in situ by the action of prostaglandin endoperoxide synthetase (PES) on the substrate 5,8,11,14-eicosatetraenoic acid (20:4). Exogenous PGG2 or 15-hydroperoxyeicosatetraenoic acid could also initiate the cooxygenation of BP, while the hydroxy compound PGH2 was inactive. Non-lipid hydroperoxides possessed very low activities in this system. Heme and certain hemeproteins stimulated cooxygenation of BP. This stimulation was predominantly the result of the inherent peroxidase activity of these agents in that they are themselves able to catalyze hydroperoxide-dependent cooxygenations. 20:4-dependent cooxygenation could be markedly inhibited by indomethacin, a PES inhibitor, supporting the role of PES in cooxygenation. The system was also sensitive to antioxidant inhibition. The isolated products of BP cooxygenation are the 1,6-3,6-, and 6,12-quinones. No intermediates mutagenic to Salmonella typhimurium strains TA98 and TA100 were detected. The BP derivatives, 7,8-dihydroxy-7,8-dihydro-BP (7,8-diol) and 7,8-dihydro BP (H2BP) were both activated by cooxygenation to intermediates highly mutagenic to TA98 and TA100. (no Refs)

13. CHEMICAL AND ENZYMATIC OXIDATION OF ALKYLATED BENZO[A]PYRENES.

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Dept. Chemistry, Ohio Univ., Athens, OH, 45701
Chem Biol Interact; 40(2):177-191 1982

The chemical and enzymatic oxidations of 6-, 7-and 10-methylbenzo[a]pyrenes, 6,10-and 7,10-dimethylbenzo[a]pyrenes and benzo[a]pyrene (BP) itself have been investigated to study the effects of alkyl substitution on the pathways of oxidation. The chemical oxidizing systems employed were Fenton's reagent (FeSO4/H2O2), trifluoroacetic acid-hydrogen peroxide (TFA/H2O2); thallium tristrifluoracetate in trifluoroacetic acid (TTFA/TFA) and H2SO4. The enzymatic systems were horseradish peroxidase (HRP/H2O2) and rat liver microsomes. The oxidations were investigated by electron paramagnetic resonance (EPR) spectroscopy to detect radical intermediates and by high performance liquid chromatography (HPLC) to separate the products. All the compounds studied produced radicals, identified as cationic species, in both H2SO4 and TTFA/TFA. In addition the 7-methyl-, 10-methyl- and 7,10-dimethyl-

BP's produced 6-oxy radicals in some or all of the remaining oxidizing systems. Both chemically and enzymatically these same three compounds were observed to produce quinones as stable products. Microsomal oxidations gave the broadest range of products exhibiting HPLC peaks in the diol, quinone and phenol regions of the chromatograms, however, there were considerable differences between products from the individual derivatives and those from the parent molecule. 6-Methyl and 6,10-dimethyl-BP's showed no evidence of oxy radical intermediates or quinones under any set of conditions, the 6-substituent effectively blocking this oxidation pathway. The observations are consistent with the expected effects of alkyl substituents at particular positions and indicate that studies such as this one are potentially useful in better understanding oxidation and possible activation pathways of polycyclic aromatic hydrocarbons. (Author abstract) (35 Refs)

14. DIFFERENTIAL ABILITY OF AMBYSTOMA TIGRINUM HEPATIC MICROSOMES TO PRODUCE MUTAGENIC METABOLITES FROM POLYCYCLIC AROMATIC HYDROCARBONS AND AROMATIC AMINES.

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Sloan Kettering Inst. Cancer Res., 145 Boston Post Road, Rye, NY, 10580
Cancer Lett; 16(1):33-41 1982

The ability of salamander hepatic microsomal mixed function oxygenases to metabolize benzo(a)pyrene (BP), perylene and the aromatic amines 2-aminoanthracene (AA), 2-aminofluorene (AF), 2-acetylaminofluorene (AAF), 4-amino-trans-stilbene (AS), monoacetylbenzidene (MAB), and diacetylbenzidine (DAB), to chemical species capable of inducing revertants in Salmonella typhimurium was investigated. Microsomal enzyme preparations from the livers of Aroclor-induced salamanders mediated the activation of AA, AF, AAF, AS, MAB, and DAB. Benzidene and 4-aminobiphenyl were poorly mutagenic in this system. The reactions were NADPH- and microsomal enzyme concentration-dependent. Rat microsomal enzyme induction with phenobarbital produced a marked increased in mutagenesis by benzidine, MAB, and DAB. However, phenobarbital was not a more effective inducer than Aroclor in the activation of these or other tested aromatic amines by salamander enzymes. No evidence was observed that BP or perylene were mutagenic after reaction with salamander liver microsomes. It is suggested that amphibian microsomal oxygenases may carry out N-oxidation more efficiently than C-oxidation. (30 Refs)

15. STEREOSELECTIVE FORMATION OF BENZ(A)ANTHRACENE (+)-(5S,6R)-OXIDE AND (+)-(8R,9S)-OXIDE BY A HIGHLY PURIFIED AND RECONSTITUTED SYSTEM CONTAINING CYTOCHROME P-450C.

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Biochem Biophys Res Commun; 106(2):602-609 1982

The enantiomeric purity and absolute configurations of the 5,6-and 8,9-oxides formed from benzo(a)anthracene (BA) upon incubation with a highly purified and reconstituted system containing cytochrome P450c were investigated. Exceptionally high stereoselectivity in the metabolism of BA to its 5,6-and 8,9-oxides by the reconstituted system was observed. Opposite stereoheterotopic faces of the hydrocarbon must have been epoxidized in order to form the observed enantiomers, a result predicted by a recent theoretical model of the steric requirements of the catalytic site of cytochrome P450c. Since liver microsomes from 3-methylcholanthrene-treated rats formed almost exclusively the (-)-(8R,9R)-enantiomer of the 8,9-dihydrodiol in other studies, it was presumed that epoxide hydrolase must selectively add water with inversion of configuration at the 9-position of the (+)-(8R,9S)-oxide. Eighty percent of the 5,6-dihydrodiol formed has been previously shown to have the (+)-(5R,6R) configuration and 20% the (-)-(5S,6S) configuration. The present study has established that epoxide hydrolase has a fourfold preference for attack with inversion at the (5S)-carbon relative to the (6R)-carbon, since the 5,6-dihydrodiol was formed from pure enantiomers (+)-(5S,6R)-oxide. (26 Refs)

BINDING TO CELLULAR MACROMOLECULES

16. SIMILARITIES IN THE FORMATION AND REMOVAL OF COVALENT DNA ADDUCTS IN BENZO(A)PYRENE-TREATED BALB/3T3 VARIANT CELLS WITH DIFFERENT INDUCED TRANSFORMATION FREQUENCIES.

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Cancer Res; 42(7):2644-2650 1982

Classes of cell variants isolated from BALB/3T3-A31 clone 1 showing high, intermediate, and low susceptibility to UV light-induced transformation also demonstrated a differential response to benzo(a)pyrene (BP)-induced transformation. On the other hand, these variants showed an identical susceptibility to the killing effect of these carcinogens. The extent of BP binding to DNA was found to be very similar in all three classes of variants under transforming conditions. BP:DNA adducts from the variant cells were analyzed by high-pressure liquid chromatography. The same adducts (N2- *10S-[7R,8S,9R-trihydroxy-7,8,9-10 tetrahydrobenzo(a)pyrene]yl* deoxyguanosine and a minute amount of the 7S enantiomer) were detected in the highly susceptible, the intermediately susceptible, and the resistant variant clones. Removal of the BP:DNA adduct occurred at an equally slow rate in all three classes of variant cells. These results indicate that the formation of stable covalent DNA adducts is not a sufficient condition for induction of transformation. Processes other than formation and removal of the stably bound BP:DNA covalent adducts are thus major factors controlling the susceptibility of BALB/3T3-A31 clone 1 variant cells to BP-induced transformation. (Author abstract) (46 Refs)

17. INTERACTION OF BENZO(A)PYRENE AND ITS DIHYDRODIOL-EPOXIDE DERIVATIVE WITH NUCLEAR AND MITOCHONDRIAL DNA IN C3H10T1/2 CELL CULTURES.

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Cancer Res; 42(7):2764-2769 1982

To analyze the distribution of radioactive carcinogens and [3H]thymidine between nuclear DNA (nDNA) and mitochon-

drial DNA (mtDNA), we have developed a simple and rapid method for the separation of nDNA and mtDNA using gel electrophoresis of cell lysates. Using this method, we found that, when C3H10T1/2 cells are exposed to either 0.5 uM [3H]-(+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a)pyrene ([3H]BPDE) or 1 uM [3H]benzo(a)pyrene, the mtDNA contains a major fraction of the total adducts formed with cellular DNAs. Deoxynucleoside adducts formed between benzo(a)pyrene and mtDNA in intact C3H10T1/2 cells or between BPDE and isolated rat liver mtDNA were analyzed by high-performance liquid chromatography, and were found to be much more heterogeneous than those present in nDNA of C3H10T1/2 cells. The extensive modification of mtDNA with BPDE in C3H10T1/2 cells is associated with preferential inhibition of the incorporation of [3H]thymidine into mtDNA when compared to incorporation of [3H]thymidine into nDNA. To analyze the factors responsible for the extensive modification of mtDNA by BPDE, we investigated the role of a lipid phase mitizing liposome:DNA complexes as a model system. We found that the liposomes protect BPDE from spontaneous hydrolysis and enhance the extent of DNA modification at low DNA concentrations. These findings extend previous evidence suggesting that the mitochondria may be important cellular targets in the process of chemical carcinogenesis. (Author abstract) (29 Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

18. THE REGIONAL LYMPH NODE (RLN) RESPONSE TO CHEMICAL CARCINOGENESIS IN THE HAMSTER CHEEK POUCH (HCP) (MEETING ABSTRACT)

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Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

The prognostic significance attributable to morphological changes in RLN draining sites of human primary cancer is somewhat variable and often contradictory. Data obtained from a variety of experimental models are of questionable value given the predilection for the use of transplanted tumors in heterotopic sites and the short durations studied. Few reports have documented the in situ RLN response to the development of induced primary carcinomas with proven metastatic potential. The present study employed stereological and histochemical techniques to monitor the morphological response of RLN to DMBA (7,12-dimethylbenz(a)anthracene) carcinogenesis in the HCP over a 24 week period. The early response, in both node and pouch, is consistent with the inductions of contact hypersensitivity to DMBA, the associated and marked paracortical (PC) expansion persisted throughout the stages of carcinogenesis (ie hyperplasia, dysplasia carcinoma). Coincident with the emergence of exophytic tumors, the RLN showed prominent follicular cortical (FC) activity and plasma cell production; this pattern of FC proliferation was superimposed on the notably expanded but relatively inactive PC compartment during the period from 12-24w. (2 Refs)

19. BLOOD VESSEL FREQUENCY DURING EXPERIMENTAL EPIDERMAL CARCINOGENESIS (MEETING ABSTRACT)

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Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

The vascularization of tumors seems to be essential for their continued growth and development, but there is relatively little information on the way the vessels develop in the vicinity of neoplasms. Using morphometric methods, we have previously reported progressive increases in the volume of blood vessels during experimental skin carcinogenesis. These methods enable the generation of objective data from histological sections. Estimates of volumetric alterations are limited in that they do not provide a complete description of the changes. In the present report, we have estimated blood vessel frequency (number per unit section area), which will enable us to determine whether the changes are a result of blood vessel dilatation or of new blood vessel production. Male Syrian golden hamsters were treated three times per week with DMBA (dimethylbenzanthracene) in liquid paraffin. Two groups of animals were used as controls, one of which was untreated and the other receiving topical applications of liquid paraffin for 10 weeks. Histological sections were prepared and using an image analyzer, the number of vessels per unit section area of dermis and hypodermis was quantified. There were progressive and significant increases in the frequency of blood vessels during skin carcinogenesis. (no Refs)

20. LUNG CANCER HISTOGENESIS FOLLOWING IN VIVO BRONCHIAL INJECTIONS OF 20-METHYLCHOLANTHRENE IN DOGS.

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Recent Results Cancer Res; 82:69-86 1982

Changes in the bronchial epithelium of dogs during carcinogenesis induced by in vivo bronchial injections of 20-methylcholanthrene (MC) were observed by fiberoptic bronchoscopy and by cytological, histological, and cytochemical analyses. Histomorphologic and cytomorphologic descriptions of normal and altered bronchial cells are given. In dogs given weekly intrabronchial injections of 50 g MC, mild atypical metaplasia was observed 1 wk after the first injection, moderate atypia was seen after 3 wk, severe atypia after 5 wk, and carcinoma in situ after 9 wk. Invasive squamous cell carcinoma was diagnosed cytologically and histologically 21 wk after first injection. Nuclear atypia increased progressively during the carcinogenic process. In dogs given a single 50 g intrabronchial injection of MC atypical basal cell hyperplasia was observed 1 day after injection. These alterations disappeared after 4 days and were successively replaced by immature and/or squamous metaplasia. Regression to mild or regular metaplasia occurred within 4-8 wk. Fiberoptic bronchoscopic findings were normal in regular metaplasia, but paleness of the bronchial mucosa was seen in mild atypical metaplasia. In carcinoma in situ irregularity in addition to dullness and thickening was found. Hyperemia, bleeding, severe thickening and irregularity were seen in invasive carcinoma. Metaplastic cells with mild atypia showed DNA contents mainly between the diploid and triploid range. In severe atypical metaplasia cytophotometric analysis showed

a heteroploid DNA distribution without any cells in the diploid region. In carcinoma in situ and in invasive squamous cell carcinoma the same heteroploid DNA distribution was observed. (34 Refs)

21. PATHOGENESIS OF BRONCHIAL CARCINOMA, WITH SPECIAL REFERENCE TO MORPHOGENESIS AND THE INFLUENCE ON THE BRONCHIAL MUCOSA OF 20-METHYLCHOLANTHRENE AND CIGARETTE SMOKING.

Nasiell M, Carlens E, Auer G, Hayata Y, Kato H, Kosaka C, Roger V, Nasiell K, Enstad I
Dept. Pathology, Sabbatsberg Hosp., Box 6401, S-11382 Stockholm, Sweden
Recent Results Cancer Res; 82:53-68 1982

The progressive epithelial cell changes occurring in squamous cell carcinoma of the lung are described. The pathogenesis of bronchogenic carcinoma may include epithelial cell injury, squamous metaplasia, various degrees of atypical metaplasia (dysplasia), carcinoma in situ, and invasive carcinoma. The initiation phase seems to be characterized by an epithelial injury with basal cell hyperplasia or cleavage - slit formation of the bronchial epithelium, with heavy loss (exfoliation) of degenerated columnar cells resulting in unprotected, nonciliated, low epithelium. The resulting low nonciliated epithelium with its unprotected surface may be sensitive to carcinogens in the mucus, which will not be removed properly. Only 10% of 211 patients with abnormal columnar cell findings had neither squamous metaplasia nor carcinoma. These results may indicate a close relationship between epithelial cell injury, abnormal columnar cell findings, and squamous metaplasia as well as bronchial cancer. Cellular atypia in the bronchial epithelium usually occurs in metaplastically altered epithelium. Mild and also moderate epithelial atypia can be induced by noncarcinogenic agents, but severe atypia can only be induced by carcinogenic agents. Carcinoma in situ (early bronchogenic squamous cell carcinoma), the sequential occurrence of abnormal bronchial cells in an experimental system, and the possibility that 'cigarette cancer' pathogenesis may be a two-step process are also discussed. (50 Refs)

22. BENZO[A]PYRENE AND OTHER INDUCERS OF CYTOCHROME P1-450 INHIBIT BINDING OF EPIDERMAL GROWTH FACTOR TO CELL SURFACE RECEPTORS.

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Carcinogenesis; 3(5):505-510 1982

The binding of 125I-labeled epidermal growth factor (EGF) was utilized to monitor possible cell surface effects of polycyclic aromatic hydrocarbon carcinogens. Exposure of confluent C3H 10T1/2 mouse fibroblasts to 1 uM benzo[a]pyrene led to a time-dependent decrease of EGF binding. By 24 hr, EGF binding was only 5% that of control cultures. In contrast, benzo[a]pyrene-7,8-diol-9,10-oxide did not significantly alter EGF binding, indicating that the inhibition by benzo[a]pyrene was not simply due to DNA damage. A curvilinear Scatchard plot in the control cells was consistent with the presence of two classes of EGF receptors having differing affinities. Our results suggest that the major effect of benzo[a]pyrene was a reduction in receptor number rather than affinity, although other interpretations have not been excluded. Progesterone, 17beta-estradiol, benzo[e]pyrene, cholesterol, phenobarbital, 1,1-bis-(p-chlorophenyl)-2,2,2-trichloroethane, hexachlorobenzene or pregnenolone-16alpha-carbonitrile, did not inhibit EGF binding. On the other hand, several known inducers of P1-450 were very effective inhibitors of EGF binding. These included: dimethylbenz[a]anthracene, 3-methylcholanthrene, benzo[a]pyrene, benz[a]anthracene, beta-naphthoflavone and alpha-naphthoflavone. We postulate that the binding of certain polycyclic aromatic hydrocarbons to the Ah receptor may induce not only specific drug metabolizing enzymes but also inhibition of EGF binding, and possible other cell effects. Further studies are required to verify this hypothesis. (Author abstract) (41 Refs)

23. THE INFLUENCE OF DIMETHYLBENZANTHRACENE (DMBA) ON FIRST GENERATION RAT MAMMARY GLAND NUCLEIC ACID CONTENT DURING LACTATION.

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Dept. Physiological Sciences, Pennsylvania Coll. Podiatric Medicine, Philadelphia, PA, 19107
IRCS Med Sci [Cancer]; 9(8):712 1981

Direct evidence that the deleterious effects of dimethylbenzanthracene (DMBA) are passed on in mother's milk from one generation to another in rats is presented. Significant decreases in mammary gland nucleic acid contents were observed on day 21 of lactation in F1 experimental rats whose mothers were injected with DMBA during pregnancy. DMBA enhanced mammary gland involution. (7 Refs)

24. CARCINOGEN-MEDIATED AMPLIFICATION OF SPECIFIC DNA SEQUENCES.

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J Cell Biochem; 18(2):149-156 1982

The development of an experimental system model, which utilizes simian virus 40 (SV40) transformed Chinese hamster embryo cells, coupled with a highly sensitive in situ hybridization procedure for the detection of a single cell in which viral DNA synthesis has been induced, is presented. When exposed to chemical carcinogens such as benzo(a)pyrene, N-methyl-N'-nitro-N-nitrosoguanidine, 7, 2-dimethyl benz(a)anthracene (DMBA), ethyl methanesulfonate aflatoxin B1, and 3-methylcholanthrene or physical carcinogens (gamma or UV radiation), SV40 DNA synthesis was induced in treated cells. Noncarcinogenic compounds such as phenanthrene and dibenz(a,c)anthracene had no effect. While carcinogen-induced amplification of SV40 DNA sequences is controlled by the viral 'A' gene, no infectious virus or complete SV40 DNA molecules were found in treated cells. DMBA treatment induced a heterogenous collection of DNA molecules with SV40 sequences. Analysis of Hirt's supernatant using restriction enzyme analysis of the amplified DNA molecules indicated that not all sequences in the integrated SV40 inserts are present. Amplification of SV40 DNA sequences may reflect a more general gene amplification phenomenon mediated by chemical carcinogens. (19 Refs)

25. CONCENTRATION DEPENDENT ALTERATIONS OF DNA REPLICATION INITIATION AND ELONGATION BY BENZO[A]PYRENE DIOL EPOXIDE.

Bowden GT, McGovern V, Ossanna N, Rosenthal H
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Carcinogenesis; 3(5):473-480 1982

Vero cells treated with various concentrations of (+)7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy, 7,8,9,10-dihydrobenzo[a]pyrene (BP-diol epoxide I) exhibited dose-dependent inhibition in both the rate of DNA synthesis and in the size of nascent DNA. The max inhibition was seen 2-3 hr after addition of BP-diol epoxide I. A recovery in both the rate of synthesis and size of nascent DNA was observed 5-10 hr after treatment. The pH step alkaline elution assay which separates different nascent DNA replication intermediates was used to investigate whether the inhibition and recovery noted above could be accounted for by alterations in DNA replication initiation (DNA synthesis within a replicon) or elongation (rejoining of replicons). At lowest dose studied (0.166 uM BP-diol epoxide I) a reversible inhibition in DNA initiation was observed. At the higher dose levels (0.66 uM and 1.66 uM BP-diol epoxide I) inhibition of both DNA initiation and elongation were observed and inhibition of elongation predominated. The inhibition in elongation was detected by an increase in the relative amount of low mol wt nascent DNA associated with DNA synthesis within a replicon and a relative decrease in the higher mol wt elongated DNA. A reversal in the inhibition of both initiation and elongation was noted. (Author abstract) (26 Refs)

26. EFFECT OF 3-METHYLCHOLANTHRENE ON RNA POLYMERASE AND PROTEIN KINASE ACTIVITIES OF TRANSCRIPTIONALLY ACTIVE CHROMATIN SUBFRACTION IN RAT LIVER.

Szeberenyi J, Kleeberg U, Tigyi A
Dept. Biology, Univ. Medical Sch., Pecs, Hungary
Experientia; 38(6):687-689 1982

The activities of RNA polymerases and nuclear protein kinases were determined in subfractions of rat liver nuclei after a single dose of the polycyclic aromatic hydrocarbon 3-methylcholanthrene (3-MC). Both enzyme activities as well as the in vivo phosphorylation of chromatin proteins were enhanced by 3-MC in the transcriptionally active subfraction of chromatin. (Author abstract) (18 Refs)

27. DISSOCIATION OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND 3-METHYLCHOLANTHRENE-INDUCED INDUCTION IN ORNITHINE DECARBOXYLASE AND ARYL HYDROCARBON HYDROXYLASE ACTIVITIES IN C57BL/6 MOUSE DERMAL FIBROBLASTS IN CULTURE.

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Cancer Lett; 16(1):25-31 1982

The effects of 3-methylcholanthrene (MC) on ornithine decarboxylase activity and of 12-O-tetradecanoylphorbol-13-acetate (TPA) on aryl hydrocarbon hydroxylase activity (AHH) in fibroblasts derived from polycyclic aromatic hydrocarbon-responsive C57BL/6 (B6) mouse dermis were investigated. While addition of TPA induced ODC activity eight-fold at 6 hr, inclusion of 2 uM MC had no effect on ODC activity. MC did, however, enhance AHH activity about five-fold at 24 hr, whereas TPA had no effect on AHH activity. Inclusion of DL-alpha-difluoromethyl ornithine (DFMO), a highly selective, irreversible inhibitor of ODC in the medium resulted in about 90% inhibition of ODC activity without affecting AHH activity. Inhibitors of microsomal monooxygenase (alpha-naphthoflavone and SKF 525 A) inhibited AHH induction by 50% and 30% and ODC induction by 73% and 100%, respectively. Indomethacin enhanced ODC activity while slightly inhibiting AHH induction. Differential sensitivity of these two enzymes to cycloheximide was also observed. Exposure of cells to DFMO resulted in a near total abolition of ODC activity, while the inducibility of AHH was not affected. ODC and AHH induction processes are thus independent of each other. (20 Refs)

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

28. MUST INITIATORS COME FIRST? TUMORIGENIC AND CARCINOGENIC EFFECTS ON SKIN OF 3-METHYLCHOLANTHRENE AND TPA IN VARIOUS SEQUENCES.

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Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Br J Cancer; 45(6):912-920 1982

Groups of hairless mice were treated with four skin applications of 470 nmol 3-methylcholanthrene (MCA) in benzene and four of 20 nmol 12-O-tetradecanoylphorbol-13-acetate (TPA) in various sequences, twice a wk, together and separately. Three days after the last application, cell kinetic investigations were made comprising the counting of basal and suprabasal cells, the assessment of hyperplasia, the mitotic rate by the stathmokinetic method, the labeling index and the specific activity of DNA after injection of a dose of [3H]dT, and the determination of percentage of cells in each cell cycle phase by flow cytometry. These studies showed that the various treatment schedules with four applications stimulated proliferation and caused epidermal hyperplasia, but there was no significant difference between the groups in degree of growth stimulation. There was a significantly higher tumor production by all the combinations than by MCA alone. It was of no significant importance for the tumor production whether the four applications of MCA came before or after the four of TPA. Alternating treatment (MCA TPA, etc) seemed to give a higher risk than the other treatment sequences. The consequences of these results for the two-stage theory of carcinogenesis (stating that initiation must come first) are discussed, and it is concluded that (at least under the experimental conditions used here) initiation does not need to come first for a good tumor yield. (Author abstract) (32 Refs)

29. RETINOIC ACID PROMOTION OF PAPILLOMA FORMATION IN MOUSE SKIN.

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Lab. Cellular Carcinogenesis and Tumor Promotion, NCI, Building 37, Room 3A21, Bethesda, MD, 20205
Cancer Lett; 16(1):1-5 1982

In a study to determine if inhibitors of tumor promotion could act by selectively killing initiated cells, mice were treated topically 3x weekly for 20 wk with 5 1 ug retinoic acid (RA) after initiation by a single application of 50 ug dimethylbenz(a)anthracene (DMBA), but before tumor promo-

tion with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) was begun. In the DMBA-initiated control, Group 1, no papillomas were observed during 20 wk of treatment with acetone solvent. The first papillomas were seen at wk 29, 5 wk after TPA promotion had begun. At wk 44, 1 wk after the termination of TPA, 93% of the mice had developed at least one papilloma, with an av of 12 papillomas per mouse. In Group 2, initiated with DMBA and treated with RA from wk 4 to wk 23, papillomas were first seen at wk 20. By wk 24, 24 papillomas had appeared in the 29 animals. Papilloma incidence at wk 24 was the result of treatment with only DMBA and RA. With continued TPA promotion, papillomas appeared somewhat more rapidly in the RA-treated mice, indicating that RA has a definite tumor promoting effect. (16 Refs)

30. EFFECTS OF DIETARY AND IN VITRO 2(3)-T-BUTYL-4-HYDROXYANISOLE AND OTHER PHENOLS ON HEPATIC ENZYME ACTIVITIES IN MICE.

Rahimtula AD, Jernstrom B, Dock L, Moldeus P
Dept. Biochemistry, Memorial Univ. Newfoundland, St. John's, Newfoundland A1B 3X9, Canada
Br J Cancer; 45(6):935-944 1982

Six phenols [2(3)-t-butyl-4-hydroxyanisole (BHA), 2-t-butylphenol, 4-methoxyphenol, 4-methylmercaptophenol, 4-butylhydroquinone and 2,6-di-t-butylphenol] previously shown to be inhibitors of benzo(a)pyrene-induced neoplasia, were examined for their ability to induce in vivo changes in hepatic mono-oxygenase and detoxication enzyme activities, and to act as mono-oxygenase inhibitors when added in vitro. (1) Generally it was found that cytochrome P450 levels were depressed, only 2,6-di-t-butylphenol caused a two fold induction (2) Mono-oxygenase activities were significantly altered; BHA and 2,6-di-t-butylphenol caused microsomes to show substantial increases in aniline hydroxylase and peroxidase activities. These microsomes, along with 4-methoxyphenol microsomes, also showed a substantial reduction in DNA binding of benzo(a)pyrene (BaP) metabolites relative to metabolism. (3) Detoxication enzymes glutathione S-transferases and epoxide hydratase were readily induced, the order of effectiveness being: BHA approx = 2,6-di-t-butylphenol greater than 4-methoxyphenol greater than 2-t-butylphenol approx = 5-butylhydroquinone (4-methylmercaptophenol failed to induce). (4) In vitro ability to inhibit BaP metabolism and DNA-binding ability was: 2,6-di-t-butylphenol greater than or equal to BHA approx = 2-t-butylphenol greater than 5-butylhydroquinone greater than 4-methylmercaptophenol greater than 4-methoxyphenol. (5) Ability in vitro to discharge the activated oxygen complex of cytochrome P450 was: 2,6-di-t-butylphenol approx = 2-t-butylphenol greater than BHA greater than t-butylhydroquinone greater than 4-methylmercaptophenol greater than 4-methoxyphenol. The results are consistent with the theory that inhibition of neoplasia is related to inducibility of detoxication enzymes, though alterations in cytochrome P450 could play a significant role in some cases. (Author abstract) (39 Refs)

31. INFLUENCE OF DAILY SUBCUTANEOUS ADMINISTRATION OF 6-METHYLPREDNISOLONE AND ORAL APPLICATION OF 30% SALINE SOLUTION ON TUMORIGENESIS INDUCED IN MOUSE STOMACH BY SINGLE APPLICATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Wagner G, Habs M, Schmahl D
(c/o Habs) Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
J Cancer Res Clin Oncol; 103(2):207-209 1982

Low dose dimethylbenz(a)anthracene (25 mg/kg po by gavage on day 1) produced papillomas in the forestomach of female C57BL/6 mice treated with 6-methylprednisolone (MP: 90 mg/kg/day sc on days 1-3) and 30% NaCl (0.25 ml/animal, days 1-3, 1 hr after MP, by gavage). Hyperplasia/hyperkeratosis was observed in 5/20 animals and papilloma in 12/20 animals. Median latent period for papilloma development was 25 days. The results indicate that in an altered environment small amounts of a chemical carcinogen suffice to induce tumors. (7 Refs)

32. EFFECT OF PRAZIQUANTEL, A NEW ANTISCHISTOSOMAL DRUG, ON THE MUTATION AND TRANSFORMATION OF MAMMALIAN CELLS.

Billings PC, Heidelberger C
(c/o Heidelberger) Comprehensive Cancer Center Res. Lab., Univ. Southern California, Los Angeles, CA, 90033
Cancer Res; 42(7):2692-2699 1982

Praziquantel (PQ), a tetrahydroquinoline derivative, is a new clinically effective antischistosomal drug, which has been shown to lack or to possess very weak mutagenic activity. However, in bacteria, this compound can act as a weak comutagen that increases the mutagenicity of several chemical mutagens and carcinogens. We have found that PQ can act as a very weak comutagen in animal cells. At 10 to 50 ug/ml, PQ increased the mutagenicity of N-methyl-N'-nitro-N-nitrosoguanidine and 2-methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine dihydrochloride about two-fold in Chinese hamster V-79 cells. In C3H/10T1/2 mouse embryo cells, PQ exhibited only negligible comutagenic activity. PQ did not oncogenically transform C3H/10T1/2 cells but had a pronounced effect on 3-methylcholanthrene-induced transformation of these cells. When PQ was coadministered with or added after 3-methylcholanthrene treatment, the number of Type III foci produced was about five-fold lower than in cultures treated with 3-methylcholanthrene alone. Therefore, PQ can inhibit Type III focus formation in C3H/10T1/2 cells. (Author abstract) (16 Refs)

33. EFFECT OF THE INSECTICIDES TOXAPHENE AND CARBARYL ON INDUCTION OF LUNG TUMORS BY BENZO(A)PYRENE IN THE MOUSE

Triolo AJ, Lang WR, Coon JM, Lindstrom D, Herr DL
Dept. Pharmacology, Jefferson Medical Coll., 1020 Locust St., Philadelphia, PA, 19107
J Toxicol Environ Health; 9(4):637-649 1982

The modulating effects of toxaphene (TOX) and carbaryl (CAR) upon benzo(a)pyrene (BP)-induced lung tumors and on BP hydroxylase activity in liver and lung were investigated. Female A/J mice were fed TOX (100 or 200 ppm) or CAR (1,000 ppm) in the diet, and administered 3 mg BP po on day 7 and day 21. No control animals or animals fed TOX alone but all BP induced and BP-induced plus TOX animals developed

forestomach tumors at 12 wk. These tumors were well-developed squamous cell papillomas. While TOX alone produced no effect upon spontaneous lung tumors, feeding 100 ppm TOX to BP-induced animals caused a slight but statistically significant decrease in the incidence of lung tumors. The higher dose TOX, however, had no effect. Both TOX doses increased BP hydroxylase activity in liver but decreased it in lung. Combined TOX plus BP followed a similar pattern. Although feeding 200 ppm TOX for 20 wk alone did not affect lung tumor incidence in BP-treated mice, it markedly decreased the mean number of tumors per mouse and the percent of BP-induced lung tumors. Feeding 1,000 ppm CAR caused a modest increase in the incidence of BP-induced lung tumors. In a second experiment, however, no significant differences in lung tumor incidence were observed between control and CAR-fed mice. Feeding CAR with BP did not affect liver BP hydroxylase activity but did significantly increase the activity of this enzyme in the lung. (47 Refs)

34. INHIBITION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED TUMORS IN SYRIAN HAMSTERS BY PRIOR INFECTION WITH H-1 PARVOVIRUS.

Toolan HW, Rhode SL, Gerthy JF
Inst. Medical Res. Bennington, Bennington, VT, 05201
Cancer Res; 42(7):2552-2556 1982

Hamsters, given injections sc at birth of H-1 parvovirus and 1 mo later given a single injection of 7,12-dimethylbenz(a)anthracene, had a 38% tumor incidence compared with a 95% incidence in animals receiving 7,12-dimethylbenz(a)anthracene alone. Thus, H-1 which, it has already been shown, invokes a resistance to the incidence of spontaneous and adenovirus-induced neoplasms in hamsters also produces a suppression of a carcinogen-induced tumor in these animals; this suggests that the H-1 induced barrier to successful oncogenesis by these diverse agents has a common mechanism which, present experiments indicate, is not related to a positive or negative H-1 serology. The pathology of the 7,12-dimethylbenz(a)anthracene-induced tumors was similar for both control and H-1-infected hamsters. Although all but one of the primary neoplasms were anaplastic fibrosarcomas as reported previously by others, 25% of the affected females had, in addition, mammary adenocarcinomas, an extremely rare tumor in hamsters. (Author abstract) (26 Refs)

35. ENHANCEMENT OF DMBA INDUCED MAMMARY TUMOURS BY INTERMITTENT WHOLE BODY HYPERTHERMIA (42 C).

Lahiri T, Deomina N, Dedov II, Lahiri P
Chittaranjan Natl. Cancer Res. Centre, Calcutta, India
Endocrinol Jpn; 28(5):569-574 1981

Effects of intermittent whole body hyperthermia (42 C) on dimethyl benz-anthracene (DMBA)-induced rat mammary tumors were determined in terms of tumor growth, plasma hormone levels, and activity of pituitary prolactin cells. Female Wistar (50-55 days old) rats were used. Heat exposure resulted in significant growth stimulation of the tumors in the majority (16/20) of heat-treated rats, compared to rats maintained at 25 C. The growth of tumors was generally intensified after 2-3 wk of heat stress and at the end of 6 wk an approx seven-fold increase in tumor vol was observed. Histological examination revealed that 18/20 animals in the control group and 17/20 in the treated group had adenocarcinoma type tumors. Other tumors were fibroadenomas and they were not included into the study. Body wt and wt of adrenal glands in heat-exposed rats were increased, while the wt of uterus and thymus was decreased. Plasma estradiol level in heat stressed animals was lowered while values for total thyroxine and thyroid stimulating hormone showed no fluctuation. Serum prolactin level was significantly increased in the heat exposed group. An electron microscopy study of prolactin cell activity of pituitary revealed that in heat stressed animals the activity was greater than in rats maintained at room temperature. Results indicated that whole body hyperthermia definitely enhances DMBA-induced mammary tumors in rats and the differences in response pattern might be related to the mode of heat application, etiology, or hormonal sensitivity of tumors. (20 Refs)

36. HYPOKINESIA AS A FACTOR OF BONE TUMOR INDUCTION.

Makarov MA, Cherkasskii LA
Medical Inst., Semipalatinsk, USSR
Vopr Onkol; 28(3):77-81 1982

The effects of different periods of hypokinesia on the development of 7,12-dimethylbenzanthracene-induced osteosarcoma of shinbone were studied in 148 rabbits. The time of induction was found to decrease considerably - from 197.6 to 113.9 days. This may be attributed to hypokinesia's constituting a stress, which involves release of adrenocortical hormones, atrophy of the thymus and reduced cellular immunological vigor. (Author abstract) (10 Refs) (In RUS)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

37. EARLY SKIN RESPONSES OF HIBERNATING AND NONHIBERNATING GROUND SQUIRRELS TO TOPICAL APPLICATIONS OF DMBA.

Ruben RJ
Dept. Anatomy, M.S. 408, Hahnemann Medical Coll. and Hosp., 230 North Broad St., Philadelphia, PA, 19102
Experientia; 38(5):612-614 1982

Skin patches on hibernating and nonhibernating ground squirrels were treated with multiple topical applications of the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA). Nonhibernators showed blistering, peeling, drying, hair loss, increased vascularization and hyperpigmentation in proportion to DMBA concentration. The latter was apparently due to (a) an increased number of dermal and epidermal melanocytes and (b) the appearance of melanocytes with large coarse cytoplasmic granules. Notably, hibernators remained free of gross skin changes and were histologically similar to untreated controls. (Author abstract) (19 Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

38. SISTER CHROMATID EXCHANGE INDUCTION IN TWO CELL LINES.

Mitchell CA, Meher-Homji KM, Baker RS
Commonwealth Inst. Health, Building A27, Univ. Sydney, Sydney, N.S.W. 2006, Australia
Environ Mutagen; 4(3):257-270 1982

In the absence of the S9 metabolizing system, benzo(a)pyrene induced sister chromatid exchanges (SCE) in Chinese hamster lung (Don) cells but not in Chinese hamster ovary cells (CHO). Addition of S9 to CHO cells is necessary to obtain levels of SCE/metaphase similar to those induced in Don cells. It is suggested that Don cells still have an intact intracellular enzyme system capable of metabolizing biologically inert compounds into an active form. (12 Refs)

39. SISTER CHROMATID EXCHANGE RESPONSE OF HUMAN DIPLOID FIBROBLASTS AND CHINESE HAMSTER OVARY CELLS TO DIMETHYLNITROSAMINE AND BENZO(A)PYRENE.

Tomkins DJ, Kwok SE, Douglas GR, Biggs D
Dept. Pediatrics, McMaster Univ. Health Sciences Centre, Hamilton, Ontario L8N 3Z5, Canada
Environ Mutagen; 4(3):203-214 1982

A study was undertaken to examine the possibility that Chinese hamster ovary (CHO) and human diploid fibroblasts may not show the same sensitivity to well known carcinogens benzo(a)pyrene (BP) and dimethylnitrosamine (DMN), using a metaboli: activation system and sister chromatid exchange (SCE) analysis. Metabolic activation in the tests was accomplished with a microsomal fraction from rats induced with Aroclor 1254. The human diploid lines employed were IMR-90, WI-8, and S-3299. For both BP and DMN the human cells and CHO cells showed dose-response slopes that were significantly different from zero, except for CHO cells treated with BP for 1 hr and S-3299 cells treated with DMN. While the responses of the human and CHO cells to BP, and the responses of the human cells to BP and DMN were similar, the dose-response of the human cells to DMN was statistically less significant than that of CHO cells. Reducing the period of treatment of CHO cells from 1.0 hr to 0.5 hr had no effect on the slope of the dose-response curves for BP and DMN. The observed differences between human and CHO cells may reflect differences in the fate of metabolic intermediates of DMN. (38 Refs)

40. EFFECT OF DIESEL EXHAUST EMISSIONS, PARTICULATES, AND EXTRACT ON SISTER CHROMATID EXCHANGE IN TRANSPLACENTALLY EXPOSED FETAL HAMSTER LIVER.

Pereira MA, McMillan L, Kaur P, Gulati DK, Sabharwal PS
Health Effects Res. Lab., United States Environmental Protection Agency, 26 W. St. Clair St., Cincinnati, OH. 45268
Environ Mutagen; 4(3):215-220 1982

The genotoxic activity of diesel exhaust emissions was evaluated by means of the sister chromatid exchange (SCE) assay and the mitotic index (MI) in fetal liver cells from Syrian hamster exposed in utero. SCE was determined in pregnant hamsters in which a pellet of bromodeoxyuridine was implanted under the skin in the interscapular area on day 13 of gestation. Two hr later the test substance was administered ip; 18 hr after treatment, the animals were killed. Exposure to diesel exhaust emissions from day 5-3 of gestation did not alter SCE or MI. The positive control 100 mg/kg benzo(a)pyrene caused a doubling of SCE and a reduction of MI. A methylene chloride extract of the diesel particulate matter caused a dose-dependent increase in frequency of SCE with a doubling in incidence caused by approx 320 mg/kg, equivalent to one-quarter of the LD50. The extract and particulate matter caused a dose-dependent decrease in the MI of fetal liver. The in utero SCE analysis was demonstrated to be a sensitive assay for the detection of the genotoxic agents present in a complex mixture of an extract of diesel particulate matter (21 Refs)

41. MUTAGENIC RESPONSES OF FIVE INDEPENDENT GENETIC LOCI IN CHO CELLS TO A VARIETY OF MUTAGENS. DEVELOPMENT AND CHARACTERISTICS OF A MUTAGEN SCREENING SYSTEM BASED ON SELECTION FOR MULTIPLE DRUG-RESISTANT MARKERS.

Gupta RS, Singh B
Dept. Biochemistry, McMaster Univ., Hamilton L8N 3Z5, Canada
Mutat Res; 94(2):449-466 1982

Response of several well characterized genetic markers such as those involving resistance to thioguanine, emetine, Ouabain, 5-6-dichlororibofuranosylbenzimidazole, and methylglyoxal bisguanylhydrazone towards a number of direct and indirect-acting mutagens was assessed in proline-requiring Chinese hamster ovary (CHO) cell line. Direct-acting alkylating and DNA-adduct forming agents such as beta-propiolactone, ethyleneimine, N-nitrosomethylurea, 4-nitroquinoline-N-oxide, methyl methanesulfonate and ethyl methanesulfonate; DNA intercalating and cross-linking agents such as ICR-170, acridine orange, ethidium bromide, mitomycin C, and actinomycin D; and chemicals requiring microsomal activation in other systems such as benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, benzidine, and beta-naphthylamine were examined. The response of various agents was determined at only two or three concentrations which should have resulted in between 10-80% cell killing. Mutation frequencies of different genetic markers which were observed in the control and mutagen-treated cultures, as well as the mutagenesis significance ratio of various markers, which provide a measure of their relative mutagenic response are shown. Of the genetic loci, no one single locus showed higher response to all of the chemicals, instead, depending upon the chemical, specific loci were found to be more responsive than others. Results indicated that CHO cells possess significant capacity for the metabolic activation of many procarcinogens, and also underscore the merits of measuring the mutagenic response at multiple genetic loci in mutagen screening studies. (40 Refs)

42. MUTAGENICITY OF THE OPTICAL ISOMERS OF THE DIASTEREOMERIC BAY-REGION CHRYSENE 1,2-DIOL-3,4-EPOXIDES IN BACTERIAL AND MAMMALIAN CELLS.

Wood AW, Chang RL, Levin W, Yagi H, Tada M, Vyas KP, Jerina DM, Conney AH
Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ, 07110
Cancer Res; 42(8):2972-2976 1982

The mutagenic activities of the four optically pure (+)- and (-)-enantiomers of the two diastereomeric bay-region chrysene 1,2-diol-3,4 epoxides were evaluated in histidine-dependent strains of Salmonella typhimurium and in cultured Chinese

hamster V79 cells. In strain TA98 of S typhimurium, (-)-1alpha,2 beta-dihydroxy-3beta,4beta-epoxy-1,2,3,4 tetrahydrochrysene was 5 to 10x more active than the other three optical isomers. However, in strain TA100 of S typhimurium and in Chinese hamster V79 cells, (+)-1beta,2alpha-dihydroxy-3alpha,4alpha-epoxy-1,2,3,4 tetrahydrochrysene was the most mutagenic diol-epoxide and was from 5 to 40x more active than the other three optical isomers. The bay-region (+)- and (-)-3,4-epoxy-1,2,3,4-tetrahydrochrysene isomers had identical mutagenic activities in all three systems. These studies indicate that the presence and orientation of the hydroxyl groups play an important role in modulating the mutagenic activity of bay-region epoxides of chrysene in both bacterial and mammalian cells. (Author abstract) (31 Refs)

43. MUTAGENICITY OF ANTHRAQUINONE AND HYDROXYLATED ANTHRAQUINONES IN THE AMES/SALMONELLA MICROSOME SYSTEM.

Liberman DF, Fink RC, Schaefer FL, Malcahy RJ, Stark AA
Environmental Medical Service, Massachusetts Inst. Technology, Cambridge, MA, 02139
Appl Environ Microbiol; 43(6):1354-1359 1982

The mutagenicity of anthracene, anthraquinone, and four structurally similar compounds of each was evaluated in the Ames/Salmonella microsome assay. Anthraquinone was shown to be mutagenic for strains TA1537, TA1538, and TA98 in the absence of rat liver homogenate. The four anthraquinone derivatives tested were mutagenic for TA1537 exclusively. None of the anthracenes exhibited mutagenic activity. (Author abstract) (9 Refs)

44. IDENTIFICATION OF SOME BENZO(A)PYRENE HYDROXYLATED DERIVATIVES AND DETERMINATION OF THEIR MUTAGEN/CANCERIGEN CHARACTERS.

Vautu A, Stafidor N, Boltasu G, Vladescu E
Inst. Oncology, Bucharest, Romania
Rev Roum Biochim; 18(4):291-301 1981

Conditions were determined for the chromatographic separation on the RP-8 column of a series of hydroxylated metabolites of benz(a)pyrene from a mixture of synthetic standards. Also determined was the minimum amount identifiable by absorption spectra in UV light and by fluorescence spectra of each metabolite. The optimum amount of every metabolite needed to produce a significant number of revertants was determined in Salmonella typhimurium strains TA 98, TA 100, TA 1537, and TA 1538 with use of the Ames test. For max absorption by wavelengths in UV, the limiting concentration was 100 nanomole/ml and the relative fluorescence spectra were reproducible above 0.50 nanomole/ml. The optimum amounts of these hydroxylated derivatives necessary to detect their mutagenic and cancerigenic character in the Ames test varied between 8.2 and 32.7 nanomole/dish. In the Ames test the diol derivatives were inactive. Generally, the epoxy- and epoxy-diol derivatives gave good reversion at lower concentrations (8.2-16.4 nanomole/dish). In most cases the phenols required higher concentrations (32.7 nanomole/dish). (13 Refs)

45. MUTAGENICITY OF SOME METHYLATED BENZO[A]PYRENE DERIVATIVES.

Santella R, Kinoshita T, Jeffrey AM
Div. Environmental Science, Columbia Univ., New York, NY
Mutat Res; 104(4/5):209-213 1982

Benzo[a]pyrene (BP), 6-methylbenzo[a]pyrene (6-MeBP), 11-methylbenzo[a]pyrene (11-MeBP), and a number of methylated derivatives were tested for mutagenicity using the Salmonella typhimurium strains TA98 and TA100. 11-MeBP was more mutagenic than BP at doses of 1-5 ug/plate, correlating with its higher carcinogenic potency. 6-MeBP was the most mutagenic derivative tested and produced approx twice the number of revertants as BP. Other compounds were less mutagenic than BP. (12 Refs)

46. RELATIONSHIP BETWEEN EXCISION REPAIR AND THE CYTOTOXIC AND MUTAGENIC EFFECT OF THE 'ANTI' 7,8-DIOL-9,10-EPOXIDE OF BENZO[A]PYRENE IN HUMAN CELLS.

Yang LL, Maher VM, McCormick JJ
(c/o Maher) Carcinogenesis Lab.-Fee Hall, Michigan State Univ., East Lansing, MI, 48824
Mutat Res; 94(2):435-447 1982

Effects of the anti isomer of 7,8-diol-9,10-epoxide of benzo[a]pyrene (anti BPDE) were studied in xeroderma pigmentosum XP12BE and normally excising diploid human cells (NF). To determine if the time available for excision repair prior to onset of semi-conservative DNA replication plays a significant role in decreasing the potentially mutagenic effect of anti BPDE, NF cells were synchronized by density inhibition, released, and treated at expression densities from a common stock soln of tritiated anti BPDE approx 16 or 1 hr prior to onset of S. The NF cells treated in situ just prior to S exhibited the highest frequency of induced mutations. The frequencies observed in NF cells treated in situ in early G1 approx 16 hr prior to S or treated in density-inhibited G0 state were significantly (12-to 16-fold) lower than those of NF cells treated just prior to S. No such difference was observed in the excision repair-deficient XP12BE cells. Results supported the hypothesis that the number of DNA lesions remaining unexcised during S determines the mutagenic effect of the agent. Results indicated that DNA replication occurred on templates containing unexcised residues and that the number of anti BPDE adducts remaining unexcised was approx the same in the replicated and the non-replicated fraction of parental DNA. At the onset of S, the number remaining bound in NF cells was approx 2.5 residues/10(6) nucleotides. (14 Refs)

47. RESTING STATE DEPTH AND SATURATION DENSITY AS MODULATED BY TUMOR PROMOTERS AND CULTURE CONDITIONS: RELATIONSHIP TO CHEMICAL TRANSFORMATION IN C3H/10T1/2 CELLS.

Mirka D, Boxmann HB
Dept.Pharmacology and Toxicology, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
JNCI; 68(2):259-266 1982

With the use of cultures of C3H/10T1/2 fibroblasts, the relationships of saturation density and cell resting state (G0) depth to oncogenic transformation by 3-methylcholanthrene (MCA) were investigated. The tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA), caused a small increase in the saturation density, but saccharin (SAC), a suspected promoter, did not Correspondingly, TPA tested positively as a promoter of transformation in a typical two-stage transformation assay with these cells while SAC did not. By altering the confluent-phase serum concentration and/or the medium renewal frequency of MCA-treated cultures, it was found that the magnitude of transformation for a given concentration of MCA was independent of the saturation density. Oscillations in this density were observed even when the medium was renewed as frequently as every 3 days, indicating that cell death

and replacement occur during what is generally regarded to be a period of cellular stability. Neither TPA nor SAC blocked the cells from progressing into deeper resting states over time, as indicated by the preneplicative lag time after a medium change at 42 days. However, the serum concentration and medium renewal frequency did affect the resting state depth. Daily renewals with medium containing 10% serum blocked the resting state from deepening and kept the cells from achieving a saturation density. Under these circumstances, transformation was completely inhibited in MCA-treated cultures. (Author abstract) (38 Refs)

48. COMPARISON OF CELLULAR GROWTH CHARACTERISTICS OF TRANSFORMED C3H 10T-1/2 CELLS ISOLATED FROM 14 DAY COLONY AND 38 DAY FOCUS AFTER EXPOSURE TO BENZO(A)PYRENE AND 1,3 DI. DIEPOXYBUTANE (MEETING ABSTRACT).

Nelson RL, Garry VF
University of Minnesota, Minneapolis, MN, 55455
In Vitro; 18(3,part2):299 1982

Utilization of the C3H 10T-1/2 clonal cell line for morphologic transformation by chemical carcinogens has been restricted by the necessity of prolonged cultivation (4-6 weeks) before morphologic transformants can be accurately identified. In this report, we will present evidence for the observation of morphologic transformation of C3H 10T-1/2 colonies in 14 to 16 days after 24 hour carcinogen exposure to dose increments of Benzo(a)pyrene and diepoxybutane. Morphologic scoring of transformants is similar to the criteria put forward by Reznikoff et al. Overall, colony transformation frequencies appear to be lower than focus transformation frequencies by a factor of 2 at the corresponding dose. Transformed colony and foci isolates were compared for the following growth parameters at 2, 5, and 10 passages: plating efficiency, soft agar growth, doubling time and saturation density. Serial subcultivation of transformants shows marked differences in soft agar growth and saturation density patterns. Characteristically, foci isolates show rapid adaptation to soft agar growth; whereas transformed colony isolates are slowly adapted. Similar differences in the saturation density patterns of the isolates were noted. (no Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

49. A SAMPLING AND ANALYTICAL PROCEDURE FOR SKIN-CONTAMINATION EVALUATION.

Keenan RR, Cole SB
Gulf Science and Technology, P.O. Box 3240, Pittsburgh, PA, 15230
Am Ind Hyg Assoc J; 43(7):473-476 1982

A sampling and analytical technique is described for quantitating skin contaminant levels found on workers exposed to coal-derived products, including polynuclear aromatic hydrocarbons. A skin-wash sampling cup sprays cyclohexane onto a 5.0 square cm of skin. A measured amount of cyclohexane drips into a vial which can be removed and sealed for subsequent analysis of the contaminants by UV fluorescence emission spectra. (3 Refs)

50. BENZO(A)PYRENE-BINDING PROTEINS OF HAMSTER EMBRYO CELL NUCLEI: COMPARISON OF NUCLEAR ISOLATION PROCEDURES.

MacLeod MC, Measfield BK, Selkirk JK
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
J Cell Biochem; 18(4):507-513 1982

Two techniques of purifying nuclei from which benzo(a)pyrene (B?)-binding proteins are isolated are compared. One bound nuclear protein, BP32, is preferentially lost from nuclei purified by a modification of the Chauveau method. BP32 is either intranuclear or tightly associated with the nucleus. Major loss of BP32 occurs not as a result of hydrodynamic shearing produced by centrifugation through 2.2 M sucrose, but as a result of osmotic shock when the 2.2 M sucrose pellet is resuspended in a solution of much lower osmolarity (0.25 M sucrose). Due to the similarity of BP32 to nucleoplasmin from frog oocytes in terms of nuclear leakage, the possibility that BP32 may be the mammalian counterpart of nucleoplasmin is currently being explored. The functional significance of polycyclic aromatic hydrocarbon binding to nuclear proteins remains unknown. (20 Refs)

REVIEWS AND OTHER RELATED STUDIES

51. INHALATION CARCINOGENESIS: AN OVERVIEW.

Chretien J
Hopital Laennec, 42 rue du Sevres, F-75007 Paris, France
Recent Results Cancer Res; 82:1-10 1982

Environmental carcinogens and their site specific action under conditions of inhalation are considered. The main carcinogens to which man is currently known to be exposed, their mode of penetration, and the histological types of carcinoma they produce are listed. Carcinogens identified in tobacco smoke include dimethylnitrosamine, diethylnitrosamine, methylethylnitrosamine, N-nitrosopyrolidine, nitrosopiperidine, benzo(a)pyrene, methylbenzo(a)pyrene, dibenz(a,h)acridine, dibenz(a,j)acridine, dibenz(c)carbazole, Beta-naphthylamine, benzo(b)fluoranthene, benzo(j)fluoranthene, methylfluoranthene, benzo(a)anthracene, chrysene, methchrysenes, and benzo(c)phenanthrene. A complex aerosol like tobacco smoke is particularly oncogenic due to synergism between components, small size of particles, and the repetitive nature of the exposure. The list of chemical environmental inhaled carcinogens will undoubtedly grow. Difficulties experienced in the detection of environmental carcinogens are discussed. Mechanisms implicated in carcinogenesis at respiratory surfaces are briefly reviewed. (45 Refs)

52. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.

Perera FP, Weinstein IB
Div. Environmental Sciences, Columbia Univ., New York, NY, 10032
J Chronic Dis; 35(7):581-600 1982

Techniques with potential usefulness in molecular cancer epidemiology are reviewed, with special emphasis placed upon a highly sensitive assay that detects covalent binding of the polycyclic aromatic hydrocarbon benzo(a)pyrene to human DNA. Benzo(a)pyrene has assumed considerable importance among chemical carcinogens because it has proven carcinogen-

ic potency in a variety of species and tissues, it is ubiquitous in the environment, and there is extensive information regarding its metabolism and mode of action. Laboratory methods applicable to molecular cancer epidemiology include techniques to assess specific host factors that may influence susceptibility to carcinogens; assays that detect carcinogens in human tissues, cells, or fluids; assays at the cellular level of biologically effective doses of carcinogens; and methods to measure early biologic and biochemical responses to carcinogenic agents. Inherited and acquired host factors that may influence human susceptibility to carcinogens, methods for detecting and quantitating chemical carcinogens in human tissues or body fluids, markers for assessing the biologically effective dose of carcinogens in humans, potential markers for early biological and biochemical response to carcinogens in humans, and the immunoassay of benzo(a)pyrene-DNA adducts as an example of a promising marker in molecular cancer epidemiology are among topics discussed. (220 Refs)

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CHEMICAL CARCINOGENESIS

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Polycyclic Aromatic Hydrocarbons and Related Compounds

SERIES CK07 No. 82/12

DECEMBER, 1982

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EPIDEMIOLOGY AND ENVIRONMENTAL DISTRIBUTION

1. REPORT OF A PILOT PROJECT IN MOLECULAR EPIDEMIOLOGY: A PRELIMINARY STUDY OF CARCINOGEN-DNA ADDUCTS IN HUMAN SUBJECTS.

Perera FP
Columbia University, New York, NY
Diss Abstr Int [B]; 43(9):3641-B 1982

This is a report of a pilot project to assess the feasibility of using an assay for the occurrence of benzo(a)pyrene-DNA adducts as a dosimeter in future molecular epidemiological investigations of cancer causation. Benzo(a)pyrene (BaP) is a significant and increasingly pervasive environmental carcinogen linked primarily with increased risk of lung cancer in humans. Because interaction between the chemical carcinogen and

HE 20.3173/2:

DNA is presumably a critical early event in tumorigenesis, the assay for BaP-DNA adducts could be a particularly relevant dosimeter in human studies Samples of lung tissue and peripheral blood cells from a small number of hospital patients with and without lung cancer were assayed using an antibody for BaP-DNA adducts hitherto applied only to cultured human cells exposed to BaP in vitro. A questionnaire was administered to patients or next of kin in order to elicit detailed histories of exposure to BaP and to agents capable of modifying metabolism and DNA binding of BaP. DNA samples from a number of subjects, all lung cancer cases, appeared to be positive in the assay. Primarily because of the small numbers studied and the limited number of controls (patients without lung cancer), no conclusions regarding significance could be drawn from these results; nor did a clear pattern emerge between exposure histories and occurrence of the DNA adduct. Nonetheless, the pilot project demonstrated the potential usefulness of both the assay and the questionnaire and provided a basis for future molecular epidemiological study. Finally, more general aspects of the questionnaire were recommended as additions to the hospital-based cancer research data system. (no Refs)

2. OBJECTIVES AND METHODOLOGICAL APPROACHES TO HYGIENIC EVALUATION OF CARCINOGENS IN THE ATMOSPHERIC AIR.

Kireeva IS
A. N. Marzaev Res. Inst. General and Community Hygiene, Kiev, USSR
Gig Sanit; (6):10-13 1982

To evaluate the pollution of atmospheric air with carcinogens, concentrations of polycyclic aromatic hydrocarbons were monitored in 47 urban and rural localities. The highest concentration of benzo(a)pyrene (BP) was recorded in the vicinity of highways. Air pollution with BP during the winter season was significantly greater than that during the summer season. The calculated annual doses of BP were 27 ug/yr for big cities, 6-8 ug/yr was small cities, and 4 ug/yr was rural population. (.3 Refs) (In RUS)

3. POLYCYCLIC AROMATIC HYDROCARBONS IN SEWAGE, MUSSELS AND TAP WATER.

Kveseth K, Sortland B, Bokn T
Central Inst. for Industrial Res., Forskningsveien 1, Oslo 3, Norway
Chemosphere; 11(7):623-639 1982

Up to 30 polycyclic aromatic hydrocarbons (PAH) have been identified by glass capillary gas chromatography in sewage effluents, mussels, and tap water. Concentrations found have been low. Some identified compounds include benz(a)anthracene, chrysene, benzo(a)pyrene, phenanthrene, pyrene, fluoranthene, naphthalene, and carbazole. PAH accumulation rate was slow in mussels at ambient water concentrations. (22 Refs)

4. POSSIBLE POLLUTION WITH BENZO(A)PYRENE OF SOIL AND AIR IN THE VICINITY OF AGRICULTURAL MACHINES.

Iakovlev AN
Construction-Transport Inst., Ust'-Kamenogorsk, USSR
Gig Sanit; (6):74-75 1982

The role of agricultural machines in the contamination of the soil and the air with benzo(a)pyrene (BP) was determined. Exhaust of the diesel engine increased the BP levels in the soil to 0.05-0.1 ug/kg. Exhaust gases were found to account for greater than 60% of the atmospheric BP. (1 Ref) (In RUS)

PHARMACOKINETICS AND METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS

5. HEPATIC AND PULMONARY EXTRACTION OF BENZO(A)PYRENE (B(A)P) IN CONSCIOUS RATS PRETREATED WITH 3-METHYLCHOLANTHRENE (3MC) (MEETING ABSTRACT).

Wiersma DA, Roth RA
Department of Pharmacology and Toxicology, Michigan State University, E. Lansing, MI, 48824
Fed Proc; 41(3):1336 1982

Many organs participate in the clearance of xenobiotic compounds from the circulation that are eliminated by metabolism. Using a two compartment open model the pharmacokinetics of B(a)P were compared in control and 3MC pretreated rats, and in 3MC pretreated rats the ability of lung and liver to eliminate circulating B(a)P was assessed. Indwelling cannulas were placed in blood vessels so as to allow evaluation of first pass effects by lung and liver. Following pretreatment with corn oil or 3MC, a bolus of 3H-B(a)P (2 mCi, 40 nmol/kg) was injected and blood concentrations of B(a)P measured periodically over the next 5 hours. 3MC pretreatment increased the total body clearance of B(a)P from 15 +/-1 to 48 +/-6 ml/min. In 3MC pretreated rats, single pass extraction by lung and liver were determined from areas under the arterial blood concentration vs time curves following intra-arterial, intravenous or intra-hepatic portal vein administration. Extraction values for lung and liver were 33% and 20%, respectively. These results suggest that in 3MC pretreated mice lung and liver are about equal in their ability to clear B(a)P from the circulation. (no Refs)

6. CYTOCHROME P-450 AND PROSTAGLANDIN SYNTHETASE DEPENDENT METABOLISM OF (+/-)-BENZO(A)PYRENE-7,8-DIHYDRODIOL BY RAT ISOLATED PULMONARY CELLS (MEETING ABSTRACT).

Sivarajah K, Jones RC, Foote JR, Shirley JE, Eling TE
NIEHS-National Institutes of Health, Research Triangle Park, NC, 27709
Fed Proc; 41(3):1571 1982

Exposure of lung to benzo(a)pyrene (BP) produces tumors presumably derived from clara and type II cells. The metabolism of (+/-) BP-7,8-dihydrodiol (BP-7,8-diol), was studied by both the cytochrome P-450 monooxygenase system and the prostaglandin synthetase system (PGS) using isolated rat type II and clara cells. These cells were prepared from control rats or animals pre-treated with beta-naphthoflavone. Clara and type II cells metabolized BP-7,8-diol in the presence of arachidonic acid (AA) or NADPH to 7,10/8,9 BP tetrol and 7/8,9,10 BP tetrol, the known solvolysis products of BP diol epoxide I. No detectable levels of tetrols were formed from BP diol epoxide II. The rate of metabolism of BP-7,8-diol in the type II cells by the AA dependent-system was about 2 fold higher than that of the NADPH system. The metabolism of BP-7,8-diol in clara cells by the NADPH dependent-system was 2 fold higher than that of AA system. Pretreatment of animals with beta-naphthoflavone increased the metabolism of BP-7,8-diol 2 to 3 fold in clara and type II cells by both AA and NADPH dependent-systems. These results suggest that PGS and NADPH dependent metabolism vary widely between cells types. The relative contribution of these systems to chemical toxicity may depend on both the nature of the chemical and the target cell. (no Refs)

7. KINETIC ANALYSIS OF MIXED FUNCTION OXIDASES (MFO) OPERATIVE IN THE METABOLISM OF BENZO(A)PYRENE B(A)P (MEETING ABSTRACT).

Evans BL, Bunce OR, Walton L, Wade AE
Department of Pharmacology, University of Georgia, Athens, GA, 30605

Fed Proc; 41(3):1548 1982

Environmental influences of aryl hydrocarbon hydroxylase (AHH) activity of hepatic microsomes using B(a)P as substrate is complicated by the fact that B(a)P is metabolized via several pathways. We have investigated the kinetics of AHH over a substrate concentration range (0.001 to 11.98 uM) using microsomes from mice subjected to dietary stress [fat-free (FF), 20% corn oil (HF)], pretreatment with the inducer, phenobarbitol and/or the carcinogen, B(a)P and N-nitrosodimethylamine (DMN). Breaks in Lineweaver-Burk plots occurred depending on diet, drug or carcinogen pretreatment and were influenced by pH and temperature. Maximum efficiency of B(a)P hydroxylation (comparison of catalytic constants) occurred at pH 7.0 for the HF Pb group, at pH 6.5 for FF and FFPb groups, and at pH 7.4 for non-induced mice fed HF diet. As expected mice receiving HF diet and Pb metabolized B(a)P most effectively (17X FF control). Pretreatment of mice with DMN and B(a)P DMN resulted in an inability to detect kinetics in the low concentration range (.001-.17)). Breaks in Arrhenius plots occurred using microsomes from all mice except those in FF Pb group (0-58C). Energies of activation using microsomes from FF, FFPb, HFPb (low concentration) and FFPB (high concentration) were 16,370 +/-147) cal/mole. This form of kinetic analysis may be used to identify individual MFO enzymes. (no Refs)

8. ALTERATION OF TISSUE LEVELS AND METABOLISM OF BENZO(A)PYRENE BY ANTI-BENZO(A)PYRENE ANTIBODIES (MEETING ABSTRACT).

Kantrowitz JD, Flynn EJ
Department of Pharmacology, New Jersey Medical School, Newark, NJ, 07013

Fed Proc; 41(3):1549 1982

The disposition of benzo(a)pyrene (BP) in mice can be altered by the administration of anti-BP antibodies. Assay of various tissues from mice which had received 3H-BP intravenously showed that the tissue:plasma ratio for BP was less in immunized mice than in controls. Initial plasma concentrations in immunized mice were seven times higher than controls following intravenous injection of H3-BP. In addition, the rate of decay (beta phase) was much faster in the immunized group. Further inspection revealed a greater percentage of the plasma BP was protein bound in the immunized group as compared to controls. The difference in the rate of decay was primarily due to the bound form of BP (half-life of 10.4 hrs for immunized vs 20.1 hrs for control), since the difference in the half-lives of the free BP differed little (23.2 hrs vs 27.4 hrs). This greater rate of decay of BP in immunized mice was paralleled by an increase in radioactivity excreted into the gastrointestinal tract. Analysis of ethyl acetate-extractable metabolites from the GI (gastrointestinal) contents by HPLC (high pressure liquid chromatography) revealed that less parent BP was being broken down to metabolites in immunized mice than in controls. (no Refs)

9. ALTERATION OF BENZO[A]PYRENE HYDROXYLATION ACTIVITY WITH AGE IN HEPATIC AND EXTRAHEPATIC TISSUES (MEETING ABSTRACT).

Sun J, Strobel HW
The University of Texas Medical School, Houston, TX, 77025

Fed Proc; 41(3):1564 1982

Benzo[a]pyrene (BaP) hydroxylation is catalyzed by microsomes from Sprague-Dawley rat liver, lung, kidney cortex and colon at varying rates at all age points examined including 2, 4, 10, 24 and 78 weeks. In liver BaP hydroxylation is low, but present at 2 weeks and peaks at 10 weeks and declines thereafter. A similar pattern is observed when BaP hydroxylation is induced with beta-naphthoflavone (beta NF) or phenobarbital (Pb). In the extrahepatic tissues BaP activity peaks at 4 to 10 weeks, but in contrast to liver, does not decline with age, but remains approximately at the peak level. Induction with Pb or beta NF is effective at all ages in colon and kidney cortex, but only beta NF induces activity in the lung. Cytochrome P-450 levels show a quite similar profile of changes with a few exceptions. There is an apparent increase in hepatic cytochrome P-450 content at 78 weeks which is not correlated with the observed decrease in BaP activity at 24 weeks. Lung cytochrome P-450 does not increase with Pb treatment, but does increase 3-fold over uninduced levels at 24 weeks with beta NF treatment. These results suggest a role for extrahepatic drug metabolism systems in metabolism of BaP. (no Refs)

10. AGE RELATED CHANGES IN DRUG, CARCINOGEN AND EPOXIDE METABOLISM IN SKIN (MEETING ABSTRACT).

Hubbard W, Mukhtar H, Bickers DR
Department of Dermatology, Veterans Administration Medical Center and Case Western Reserve, University Cleveland, OH, 44016

Fed Proc; 41(3):1547 1982

The postnatal development of microsomal aryl hydrocarbon hydroxylase (AHH), 7-ethoxycoumarin O-deethylase (ECD) and epoxide hydrolase (EH) (BP-4,5-oxide as substrate) and cytosolic glutathione-S-transferase (GST) was investigated in the skin of male and female rats. Animals were treated with topical application of 3-methylcholanthrene (MCA; 40 mg/Kg 24 hours before sacrifice) or acetone. Measurable enzyme activities were detected in 3-day-old animals. No sex dependent differences in skin enzyme levels were observed. AHH and ECD in control animals did not show significant age-dependent variation. In 32-day animals skin AHH and ECD levels were 20-40% higher than in 4-day-old rats. Considerable differences in the inducibility of skin AHH and ECD by topically applied MCA were observed. At 4,10,18,32 and 55-days of age the inducibility of AHH was 12,14,27,29 and 21-fold, respectively. A similar pattern was observed for ECD. EH activity in 24-day-old rat skin was twice higher than in 4-day old rat skin. EH was not affected at any age by MCA. GST activity remained constant throughout maturation of the rat and was not altered by MCA. Benzo(a)pyrene (BP) metabolism was studied in control and MCA induced neonatal (4-day-old), young (15-day-old) and adult (55-day-old) animals. MCA treatment increased the metabolism of BP at all ages studied; higher rates of metabolism occurred in adult skin compared to younger or neonatal skin. These studies indicate that drug and carcinogen metabolism in skin undergo variable changes during aging. (no Refs)

11. COMPARISON OF METABOLISM OF BENZO(A)PYRENE (BP) BY HAMSTER AND RAT KIDNEY, LIVER, INTESTINE, LUNG AND TRACHEA CELLS IN CULTURE (MEETING ABSTRACT).

Raineri R, Hillesund T, Ernst MK, Polley JA
Litton Bionetics, Inc., Kensington, MD, 20895
Proc Am Assoc Cancer Res; 23:329 1982

The metabolism of BP was compared using reverse phase HPLC (high pressure liquid chromatography) and by determination of levels of covalent binding, with cultured kidney, liver, small intestine, lung and trachea from male Syrian golden hamsters and Sprague-Dawley rats. Hepatocytes from both species metabolized BP to a 3 to 5 times greater extent than the other cells studied. Formation of water-soluble metabolites by hepatocytes was at least 10 times that of the other cells, accounting for their greater activity. Generally hamster cells had greater metabolic capability than rat cells. High levels of BP-9,10-dihydrodiol and BP-7,8-dihydrodiol (12 pmoles/ml medium) were observed with hamster hepatocytes as well as with rat hepatocytes, kidney, intestine and lung cells. Levels of covalent binding of metabolites of BP were at least 10 times greater in hepatocytes from both species than in the other cell types. Binding to hepatocytes and hamster embryo cells increased with incubation time coinciding with an increase in the formation of water-soluble and diol metabolites. The metabolic potential of intact cell systems was assessed by determination of the formation of organic-soluble and conjugated metabolites, as well as of the activation of BP through covalent binding. These studies suggest the potential usefulness of these cells for metabolic activation in vitro test systems. (no Refs)

12. THE METABOLISM OF DIBENZ(A,H)ANTHRACENE (DBA) BY MOUSE HEPATIC MICROSOMES AND ITS RELATIONSHIP TO DBA-INDUCED TUMOR FORMATION (MEETING ABSTRACT).

Kouri RE, Connolly G, Nebert DW, Lubet RA
Division of Toxicology and Oncology, Microbiological Associates, Bethesda, MD, 20816
Proc Am Assoc Cancer Res; 23:337 1982

DBA metabolism by 3-methylcholanthrene-and-DBA-induced hepatic microsomes from strains of mice (C57Bl/6J, C3H/HeJ, AKR/J and DBA/2J) was determined employing reverse phase high performance liquid chromatography analysis. Two of the strains (C3H/HeJ and C57Bl/6J) showed a three to six fold greater rate of overall metabolism than strains (AKR/J and DBA/2J), and additionally, these strains showed a five to nine fold greater rate of production of DBA-3,4-dihydrodiol, the apparent precursor to the bay region diol epoxide. When animals from these strains were injected subcutaneously with 150 ug DBA in corn oil, strains C3H/HeJ and C57Bl/6J had tumor incidences of 84% and 53% respectively, while strains AKR/J and DBA/2J has incidences of less than 3% (at 12 months post treatment). Thus, there appeared to be possible association between aryl hydrocarbon hydroxylase inducibility (Ah locus) and susceptibility to DBA-induced tumors. To delineate the role of the Ah locus, classical genetic techniques employing crosses between the AHH (arylhydrocarbon hydroxylase) inducible (Ahb, C57Bl/6J strain and the AHH non-inducible (Ahd) DBA/2J strain were employed. When (B6xD2)F1 animals were challenged with DBA, their response was similar to the B6 parent (50% incidence). In contrast, (B6xD2)xD, backcross animals yielded intermediate level of tumorigenesis (27% incidence). The specific Ah phenotype of the individual (B6xD2)xD2 animals is now being tested. (no Refs)

13. THE METABOLISM OF DIBENZ(A,H)ANTHRACENE (DBA) BY MOUSE HEPATIC MICROSOMES AND ITS RELATIONSHIP TO DBA INDUCED TUMOR FORMATION (MEETING ABSTRACT).

Lubet RA, Connolly G, Nebert DW, Kouri RE
Division of Toxicology and Oncology, Microbiological Associates, Bethesda, MD, 20816
Fed Proc; 41(3):1426 1982

DBA metoblism by MCA (monoclonal antibodies) induced hepatic microsomes from four strains of mice (C57Bl/6J, C3H/HeJ, AKR/J and DBA/2J) was determined employing reverse phase HPLC (high pressure liquid chromatography) analysis. Strains C3H/HeJ and C57Bl/6 showed a three to six fold higher rate of overall metabolism than strains AKR/J and DBA/2J. In addition these strains showed a five to nine fold greater rate of production of DBA 3,4 dyhydrodiol, the apparent precursor to the bay-region diol epoxide, reflecting a shift in metabolism to the 3,4 position in MCA induced microsomes. When DBA itself was employed to induce aryl hydrocarbon hydroxylase and Ethoxyresorufin O-deethylase activities in mice the C3H and C57Bl strains were induced while the AKR and DBA/2 were not. When animals from these strains were injected subcutaneously with 150 ug DBA in corn oil strains C3H and C57Bl/6 had tumor incidences of 84 and 53% respectively, while strains AKR and DBA/2 had incidences of less than 3%. Further studies involving determinations of the roles of substrate concentration and conjugation reactions in microsomal activation of DBA will be presented. (no Refs)

14. HUMAN BREAST CELL MEDIATED MUTAGENESIS (MEETING ABSTRACT).

Gould MN, Cathers LE, Moore CJ
Department of Human Oncology, University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:317 1982

We compared the ability of human and rat mammary cells to activate chemical carcinogens. Both human and rat mammary glands were enzymatically dispersed and separated into stromal and parenchymal enriched populations. The natures of these fractions were confirmed by light and electron microscopy. Stromal and parenchymal populations from both species were cultured at varying cell densities. After the mammary cells attached, they were irradiated with 3000 rad and then cultured with V-79 cells. The co-cultures were exposed to DMBA (dimethylbenzanthracene) (1 ug/ml) for 45 hours. The cultures were then washed and the V-79 cells were removed and assayed for the induction of mutations at the HGPRT locus. Each of the four cell populations activated DMBA. The number of induced mutants was related to the density of mammary cells plated within each species. We found that both the parenchymal and stromal cells could activate DMBA to an equivalent extent, as measured by induced mutation. However, at optimal cell densities the rat cells induced about four times the number of mutations as did the human cells. In addition, we compared these cells for the ability to convert polycyclic hydrocarbons to water-soluble metabolites. Both human and rat stromal cells were more efficient at converting DMBA and BP to water-soluble products than were their respective epithelial cell populations. Rat stromal and parenchymal cells converted BP to water-soluble derivatives more efficiently than their human counterparts. (no Refs)

15. S-ADENOSYL-L-METHIONINE IS A CARBON DONOR IN THE CONVERSION OF BENZO(A)PYRENE TO 6-HYDROXYMETHYLBENZO(A)PYRENE BY RAT-LIVER S-9 (MEETING ABSTRACT).

Flesher JW, Stansbury KH, Sydnor KL
University of Kentucky Medical Center, Lexington, KY, 40536
Proc Am Assoc Cancer Res; 23:307 1982

In earlier studies we reported that 6-hydroxymethylbenzo(a)pyrene is a metabolite of benzo(a)pyrene and of 6-methylbenzo(a)pyrene when these substrates are incubated with homogenates of rat-liver. However, the exact nature of the carbon donor was not established when benzo(a)pyrene was used as a substrate. S-9 Supernatant was prepared from the livers of Sprague-Dawley male rats. Benzo(a)pyrene 100 nmole 0.6 umole NADPH, 3 umole MgCl2, 20 umole potassium phosphate buffer, pH 8.0, and 3.0 uCi S-adenosyl-L-methionine (Methyl-3H) and S-9 supernatant (2 mg liver protein) total volume 1 ml, were incubated in a light-protected Dubnoff shaker at 37C for 1 hr in air. The reaction was stopped by addition of one volume of cold acetone. After adding 6-hydroxymethyl-benzo(a)pyrene and 6-methylbenzo(a)pyrene to the mixture it was extracted 3 times with ethyl acetate. The ethyl acetate extracts were combined, washed with water and evaporated under reduced pressure. The extracted products were redissolved in 2-ethoxyethanol and analyzed by high performance liquid chromatography (HPLC). Eluant fractions were collected every minute for counting of tritium in a Packard liquid scintillation counter. The results clearly demonstrate that a radioactive product indistinguishable from authentic 6-hydroxymethylbenzo(a)pyrene is formed thereby identifying the tritium labeled compound as 6-hydroxymethylbenzo(a)pyrene. In large scale incubations using unlabelled S-adenosyl-L-methionine the identity of the 6-hydroxymethylbenzo(a)pyrene was confirmed by thin layer chromatography, HPLC and gas chromatography-mass spectrometry of a trimethylsilane derivative. (no Refs)

16. THE ROLE OF L-REGION METHYL SUBSTITUENTS IN THE METABOLIC ACTIVATION OF THE POTENT CARCINOGEN, 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA).

Watabe T, Ishizuka T
Lab. Drug Metabolism and Toxicology, Dept. Hygienic Chemistry, Tokyo Col. Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan
J Pharmacobio Dyn; 5(5):S-57 1982

7-Hydroxymethyl-12-methylbenz(a)anthracene and 12-hydroxymethyl-7-methylbenz(a)anthracene, major carcinogenic products of 7,12-dimethylbenz(a)anthracene, were activated more potently by cytosolic sulfotransferase than by microsomal monooxygenase as measured by the Ames assay. These data suggest that the sulfate ester conjugation of these derivatives plays a more important role in their activation than does microsomal epoxidation. (no Refs)

17. IN VITRO METABOLISM OF 12-METHYLBENZ(A)ANTHRACENE: EFFECT OF THE METHYL GROUP ON THE STEREOCHEMISTRY OF A 5,6-DIHYDRODIOL METABOLITE.

Fu PP, Chou MW, Yang SK
Natl. Center for Toxicological Res., Jefferson, AR, 72079
Biochem Biophys Res Commun; 106(3):940-946 1982

Metabolism of 12-methylbenz(a)anthracene (MBA) by rat liver microsomes formed a (-)trans-5,6-dihydrodiol with S,S absolute stereochemistry as the predominant enantiomer. When benz(a)anthracene (BA) was incubated under similar conditions, (+)BA trans-5R,6R-dihydrodiol was the major enantiomer formed. Thus, a methyl substituent of a polycyclic aromatic hydrocarbon may alter the stereoselective preference of the rat liver microsomal drug-metabolizing enzyme system toward the substrate molecule in the formation of a dihydrodiol metabolite at an unsubstituted aromatic double bond. (16 Refs)

18. STEREOSELECTIVE METABOLISM OF BENZ[A]ANTHRACENE (BA) TO (+)-BA (5S,6R)-OXIDE BY A HIGHLY PURIFIED AND RECONSTITUTED SYSTEM CONTAINING CYTOCHROME P-450C (MEETING ABSTRACT).

Van Bladeren PJ, Armstrong RN, Cobb D, Ryan DE, Thomas PE, Levin W, Jerina DM
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):1222 1982

A principal site of metabolism of BA by liver microsomes from 3-methylcholanthrene-treated rats is the K-region 5,6-double bond. In order to determine the absolute configuration of the 5,6-arene oxide formed, a procedure has been developed to separate the four possible isomeric glutathione conjugates (two positional isomers from each enantiomer) which were obtained synthetically from the individual enantiomeric arene oxides. When [14C]-BA was incubated with a highly purified and reconstituted monooxygenase system containing cytochrome P-450c (greater than 70% of total cytochromes P-450 in liver microsomes from 3-methylcholanthrene-treated rats) and glutathione was allowed to react with the arene oxides formed, HPLC (high pressure liquid chromatography) of the resultant adducts indicated that radioactive conjugates were formed only from the (+)-(5S,6R)-enantiomer. Insignificant amounts of adducts (less than 3%) from the opposite enantiomer were detectable. The present results as well as previous studies which established that cytochrome P-450c predominantly forms benzo[a]pyrene (4S,5R)-oxide from benzo[a]pyrene are in agreement with our theoretical predictions of the steric requirements of the catalytic binding site of cytochrome P-450c. (no Refs)

19. STEREOSELECTIVE METABOLISM OF THE (+) AND (-)-ENANTIOMERS OF TRANS-1,2-DIHYDROXY-1,2-DIHYDROCHRYSENE TO BAY REGION 1,2-DIOL-3,4-EPOXIDES BY RAT LIVER ENZYMES (MEETING ABSTRACT).

Vyas KP, Yagi H, Tada M, Thakker DR, Ryan DE, Thomas PE, Conney AH, Levin W, Jerina DM
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):1222 1982

Metabolism of (+)- and (-)-chrysene 1,2-dihydrodiols was examined to establish whether the stereoselectivity of cytochrome P-450c toward these dihydrodiols parallels that observed for the corresponding phenanthrene 1,2-and B[a]P 7,8-dihydrodiols. Microsomes prepared from control and treated rats as well as a reconstituted system containing highly purified cytochrome P-450c stereoselectively metabolized (+) and (-)-chrysene 1,2-dihydrodiols to their diastereomerically related bay-region 1,2-diol-3,4-epoxides. The extent to which diol epoxides were formed and the ratio of the two diastereomeric diol epoxides were highly dependent on both the enantiomer of the dihydrodiol and treatment of the rats. The trans diol epoxides predominated from the (-)-(1R,2R)-dihydrodiol and cis

diol epoxide predominated from the (+)-enantiomer. Microsomes from 3-methylcholanthrene (3-MC)-treated rats displayed a higher degree of regio- and stereoselectivity compared to microsomes from control or phenobarbital (PB)-treated rats. In addition to diol epoxides, a phenolic metabolite was identified from both the (+)- and (-)-dihydrodiols. This phenolic-dihydrodiol was found to be an inhibitor of metabolism of the 1,2-dihydrodiol. Both PB and 3-MC failed to induce metabolism of the dihydrodiols per nmol cytochrome P-450. (no Refs)

20. METABOLIC ACTIVATION OF BENZO(B)FLUORANTHENE IN MOUSE SKIN (MEETING ABSTRACT).

LaVoie EJ, Amin S, Juchatz A, Hecht SS, Hoffman D
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:332 1982

Benzo(b)fluoranthene (B[b]F) is a ubiquitous carcinogenic polynuclear aromatic hydrocarbon. The metabolic activation of B[b]F in mouse skin was studied using two approaches: characterization of B[b]F-DNA adducts formed in vivo and tumorigenicity assays of monofluorinated derivatives of B[b]F. 3H-B[b]F (400 uCi, 99 ug/mouse) was applied to mouse skin, after 24 hrs DNA was isolated from the treated epidermis, and enzymatically hydrolyzed to deoxyribonucleosides. Chromatography on Sephadex LH-20 revealed five bands (A-E) of radioactivity (eluting between 480-780 ml). These bands had the following percentages of radioactivity: A (12%), B (19%), C (32%), D(32%), and E (6%). Band B corresponded in elution volume to the major reaction product of B[b]F-9,10-diol-11,12-epoxide with calf thymus DNA in vitro. Approx 32% of B was also found to coelute on high performance liquid chromatography with this synthetic bay-region dihydrodiol epoxide-nucleoside marker. These results suggest that the DNA adduct from B[b]F-9,10-diol-11,12-epoxide represents a minor fraction of the DNA adducts of B[b]F formed in mouse skin. To investigate which positions of B[b]F are associated with its activation, 7-fluoroB[b]F, 9-fluoroB[b]F, and 11-fluoroB[b]F were synthesized. Metabolism studies with rat liver 9000 x g supernatant indicated that fluorine blocked dihydrodiol and phenol formation at the carbon with the fluorine atom. Each fluorinated compound was tested for tumor-initiating activity at initiating doses of 30 and 100 ug. (no Refs)

21. EFFECT OF A PERI FLUORO SUBSTITUENT ON THE CONFORMATION OF DIHYDRODIOL DERIVATIVES OF POLYCYCLIC AROMATIC HYDROCARBONS.

Chiu PL, Fu PP, Yang SK
Dept. Pharmacology, Sch. Medicine, Uniformed Services Univ. of the Health Sciences, Bethesda, MD, 20814
Biochem Biophys Res Commun; 106(4):1405-1411 1982

Evidence is presented that a peri fluoro substituent can direct the conformation of the dihydrodiol metabolite primarily because of the electronic repulsion between the electronegative fluorine and the peri hydroxyl oxygen. Four dihydrodiols were isolated by reversed-phase high performance liquid chromatography in order to confirm the conformation of the 7-fluorobenz[a]anthracene dihydrodiols. The dihydrodiols are quasi-axial with a vicinal olefinic double bond situated in a bay region thus exhibiting only weak tumorigenic activities. (15 Refs)

22. CHARACTERISTICS OF MICROSOMAL REDUCTION OF BENZO[A]PYRENE 4,5-OXIDE.

Wrighton SA, Fahl WE, Shinnick FL, Jefcoate CR
(c/o Jefcoate) Dept. Pharmacology, Univ. Wisconsin Medical Sch., Madison, WI, 53706
Chem Biol Interact; 40(3):345-356 1982

NADPH-reduction of benzo[a]pyrene 4,5-oxide (BP-4,5-oxide) to BP required four components from rat liver: cytochrome P-450, NADPH cytochrome P-450 reductase, phosphatidylcholine and a soluble, heat-sensitive factor which was present in 105,000 x g supernatant and was also released from microsomes by sonication. The requirement for this factor contrasts with recently reported results from Sugiura et al. Oxide-reduction was 40x faster under anaerobic conditions, but oxygen did not affect the stimulation factor. This stimulation was highest (x15) at low concentrations of microsomal protein (less than 0.1 mg/ml) and was almost absent at high concentrations of microsomal protein (greater than 1 mg/ml). Oxide-reduction activity was proportional to microsomal protein concentration in the presence of added 105,000 x g supernatant, but for microsomes alone (greater than 0.1 mg/ml) exhibited a parallel plot with an intercept at 0.08 mg/ml microsomal protein. Stimulation was highest at high concentrations of BP-4,5-oxide and a linear plot of V1 vs. [BP-4,5-oxide](1) was only obtained in the presence of 105,000 x g supernatant (K_m = 3uM, V_{max} = 3.3 nmol/mg/min). Microsomal hydration of BP-4,5-oxide (inhibited in reductase assays) was unaffected by 105,000 x g supernatant, suggesting that stimulation of oxide-reduction did not derive from solubilization of BP-4,5-oxide. Stimulation was observed in the initial rate of reaction and was independent of incubation time. Inhibition of lipid peroxidation, removal of peroxides and deoxygenation were all excluded as explanations of the stimulatory effect. (Author abstract) (18 Refs)

23. TIME COURSE OF METABOLISM OF BENZO[E]PYRENE BY HAMSTER EMBRYO CELLS AND THE EFFECT OF CHEMICAL MODIFIERS.

MacLeod MC, Mansfield BK, Selkirk JK
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Chem Biol Interact; 40(3):275-285 1982

In cultures of hamster embryo cells, benzo[a]pyrene (B[a]P) is metabolized primarily in the bay region. In contrast, little or no bay region metabolism of the noncarcinogenic isomer benzo[e]pyrene (B[e]P) could be detected during 12-96-h incubations of hamster embryo cells with 4uM [3H]B[e]P. The upper limit to 9,10-dihydro-9,10-dihydroxy-benzo[e]pyrene formation is about 0.2% of the ethyl acetate-soluble metabolites (less than 0.1% of the total metabolites). The major identified metabolites of B[e]P were 4,5-dihydro-4,5-dihydroxy benzo[e]pyrene and the glucuronide conjugates of 3-OH-benzo[e]pyrene and 4,5-dihydro-4,5-dihydroxy B[e]P. Simultaneous treatment of cells with either B[a]P or 7,8-benzoflavone (BF) did not induce bay region metabolism of [3H]B[e]P. (Author abstract) (27 Refs)

24. SELENIUM ENHANCED CONJUGATION OF BENZO(A)PYRENE BY HEPATOCYTES (MEETING ABSTRACT).

Marshall MV, Gonzalez MA, Griffin AC
Southwest Foundation for Research and Education, San Antonio, TX, 78284

Proc Am Assoc Cancer Res; 23:278 1982

Previous studies have attributed anticarcinogenic properties to enhanced dietary intake of selenium. No mechanism of action has yet been determined, although several reports have demonstrated enhanced detoxification of chemical carcinogens requiring metabolic activation. The purpose of this study was to investigate the detoxification of benzo(a)pyrene (BaP) by hepatocytes isolated from rats fed a selenium supplementation of 4 ppm in their drinking water. Rats were fed a control diet or one containing 4 ppm Se (as Na2SeO(3)) for 15 days. After 11 days on the experimental diet, animals in both groups (control, Se) were injected with Aroclor 1254 to induce mixed function oxidase activity. Hepatocytes were isolated 4 days later and cultured with 50 uM 3H BaP for up to 2 h. In hepatocytes isolated from the Se group, an increase in sulfate, glucuronide, and glutathione conjugation was observed. An increase in dihydrodiol and phenol formation and a decrease in quinone formation was also observed for the free metabolites. In summary, dietary Se administration enhanced the conjugation of BaP. Increases in metabolism were also observed in the free metabolite fraction. The increase in dihydrodiol production also implicates an enhancement of epoxide hydrolase activity. The overall effect was to increase conversion of BaP to water soluble metabolites and conjugates. (no Refs)

25. MECHANISMS CONTROLLING EXCRETION OF BENZO(A)PYRENE AND ITS METABOLITES BY THE SOUTHERN FLOUNDER, PARALICHTHYS LETHOSTIGMA (MEETING ABSTRACT).

Pritchard JB, Frech ME, Beno JR, Niehs CV
Whitney Laboratory, St. Augustine, FL, 32084

Fed Proc; 41(3):1545 1982

Marine teleosts extensively metabolize polycyclic aromatic hydrocarbons (PAH) via the cytochrome P-450 mixed function oxidase system. In contrast to mammals, a much greater fraction, approximately 60%, of the metabolism of the model PAH, benzo(a)pyrene (BP), occurs at the benzo-ring. Metabolism in this region of the molecule yields metabolites which have been shown to be toxic, ie carcinogenic, mutagenic. Following injection of 2.5 umol/kg radiolabelled BP, BP-7-phenol, BP-1-phenol, or BP-7,8-trans-dihydrodiol, the clearance of each compound exceeded the simultaneously measured glomerular filtration rate, thus, demonstrated net tubular secretion. Clearance of label following BP-7,8-diol administration exceeded that following the phenol metabolites by 10 fold and was more than 30 times the initial clearance after injection of BP itself. Analysis of the urine by TLC (thin layer chromatography) and HPLC (high pressure liquid chromatography) indicated that 100% of the urinary radioactivity was found in polar metabolites of the initial compound, predominantly glucuronide and sulfate conjugates. Secretion was blocked by probenecid, the classical inhibitor of the organic anion transport system. Finally, it was shown that other organic anions including the herbicide, 2,4-D, were very effective inhibitors of the secretion of these PAH metabolites, suggesting that these 'less toxic' anions might potentiate PAH toxicity by prolonging their retention and promoting bioconcentration. (no Refs)

26. MAMMALIAN ACTIVATION AND METABOLISM OF 1-NITROPYRENE (MEETING ABSTRACT).

Ball LM, Kohan MJ, Claxton L, Lewtas J
Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC, 27711

Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

We have used 1-nitropyrene (NP) as a model Nitrated polycyclic organic compound (NPOC), to investigate potential genotoxicity in mammalian systems. NP was generally non-mutagenic in bioassays conducted in Chinese hamster ovary cells, and in the mouse lymphoma L5178Y system. However with the addition of a metabolic activation system consisting of the S-9 fraction from Arochlor-induced rat liver, NP proved to be more mutagenic than benzo(a)pyrene in the latter assay. NP also induced unscheduled DNA synthesis in primary rat hepatocytes. The ability of S-9 to activate NP was confirmed by assay in the Salmonella nitro-reductase-deficient strain TA98FR1, in which NP exhibits minimal 'direct-acting' mutagenicity. S-9 increased the mutagenicity of NP seven-fold,and microsomes derived from the S-9 produced a twenty-fold increase. 1-Aminopyrene and N-acetylaminopyrene, the principal reductive metabolic products of NP, have been identified by HPLC (high performance liquid chromatography) in incubations of NP with S-9. Other metabolites were tentatively identified as phenols produced by aromatic ring oxidation. Thus some mammalian enzyme systems are indeed capable of carrying out the metabolic reactions associated with genotoxic activity in microbes. The contribution of the oxidative metabolic products to the geno- and cytotoxicity seen in mammalian cells remains to be evaluated more closely. (no Refs)

27. EVIDENCE FOR A 2,3-EPOXIDE AS AN INTERMEDIATE IN THE MICROSOMAL METABOLISM OF 6-NITROBENZO(A)PYRENE (MEETING ABSTRACT).

Fu PR, Chou MW, Evans FE, Yang SK
National Center for Toxicological Research, Jefferson, AR, 72079

Fed Proc; 41(3):1730 1982

Nitrobenzo(a)pyrene (6-NO(2)-BaP), an environmental pollutant, was found to be metabolized by rat liver microsomes to form 1 and 3-hydroxy-6-NO(2)-BaP which were more mutagenic than 6-NO(2)-BaP tested in Salmonella typhimurium tester strains TA98 and TA100 with S9 activation. This study reports that this 3-hydroxy-6-NO2 metabolite is formed in vitro through a 2,3-epoxide intermediate which rearranges spontaneously via an NIH shift mechanism. The evidence was obtained by mass and 1H NMR (nuclear magnetic resonance) spectral analysis of the major metabolite, 3-hydroxy-6-NO(2)-BaP, of metabolism of 3-deutero-6-NO(2)-BaP by rat liver enzymes. These analyses indicated that 50% of the deuterium label was retained at the C-2 position. Thus, these results indicate that ring epoxidation by the cytochrome P-450 system is involved in the metabolism of 6-NO(2)-BaP. (no Refs)

28. EVIDENCE OF ENZYMATIC REDUCTION OF 1-NITROPYRENE BY RAT LIVER FRACTIONS.

Nachman JV, Wei ET
Chevron Environmental Center, P.O. Box 1272, Richmond, CA, 94802

Experientia; 38(7):837-838 1982

1-Nitropyrene, a mutagenic compound found in diesel exhaust and photocopy toners, is reduced anaerobically by rat liver fractions to 1-aminopyrene. This reaction is stimulated in the microsomal fraction by NADPH and in the cytosol by

FMN. Addition of both cofactors produced more reduction in S-9, microsomes, or cytosol than either cofactor alone. (Author abstract) (10 Refs)

29. METABOLISM OF 6-NITROBENZO(A)PYRENE BY HAMSTER EMBRYO CELLS AND RAT LIVER MICROSOMES (MEETING ABSTRACT).

Tong S, Selkirk JK
University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:312 1982

Nitrosarenes are formed during combustion of diesel fuel. Several of these compounds are known mutagens in short-term assay and are therefore suspect as presenting a potential human risk. The metabolism of a suspected environmental contaminant, 6-nitrobenzo(a)pyrene, was studied employing hamster embryonic fibroblasts and hepatic microsomes from 3-methylcholanthrene pretreated rats to compare intact cell metabolism against cell-free systems routinely used in short-term mutagenic assays. Organic solvent-soluble metabolites were separated by high-pressure liquid chromatography. Incubation of 6-nitrobenzo(a)pyrene with hamster embryo cells gave rise to both organic and water-soluble metabolites. When ethyl acetate extract of the extracellular medium was analyzed, a major peak at the dihydroxy region was detected 24 hr after introduction of substrate to cell culture. Small amounts of a phenolic product was also obtained at this time point. Subsequent treatment of remaining aqueous phase with beta-glucuronidase, however, indicated that the majority of the phenol produced had readily been converted to water-soluble glucuronide conjugates. Intracellular metabolites of 6-nitrobenzo(a)pyrene were also detected and comprised mainly of phenolic and dihydroxy products. As a comparison to cellular metabolism, hepatic microsomes were incubated with 6-nitrobenzo(a)pyrene in the presence of NADPH. Microsomal metabolism resulted in the production of one major phenolic metabolite, which was previously found to be conjugated in the cellular system, with minor dihydroxy and quinone products. (no Refs)

30. THE COOPERATIVE ROLE OF BACTERIAL AND MAMMALIAN ENZYMES IN MUTAGENIC ACTIVATION OF NITRO-PAH COMPOUNDS (MEETING ABSTRACT).

Pederson TC, Siak JS
Biomedical Science Department, GM Research Laboratories, Warren, MI, 48090
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

The NADPH Dependent enzyme activity in rat liver microsomes can significantly increase the mutagenicity of several nitro-substituted PAH (polynuclear aromatic hydrocarbon) compounds in the Salmonella/S9 mutation assay under appropriated assay conditions. The enhanced mutagenicity of 2-nitrofluorene (2NF), 1-nitropyrene (1NP), 6-nitrochrysene (6NC) and 6-nitrobenzo(a)-pyrene (6NBaP) in the presence of S9 enzymes can be detected using strain TA98 or the nitroreductase-resistant strain TA98NR. The S9-dependent activation of 6NBaP, like that of BaP, can also be observed using the dinitropyrene-resistant strains TA98/1,8-DNP6 and TA98NR/1,8-DNP2. In contrast, there is little or no detectable activation of 2NF, 1NP or 6NC by S9 enzymes in assays employing the dinitropyrene-resistant strains, suggesting that the S9-dependent mutagenicity of these compounds towards TA98 and TA98NR requires bacterial nitroreductase activity for formation of the ultimate mutagenic metabolites. This interpretation is supported by experiments with 1NP which demonstrate that an extractable mutagenic metabolite accumulates during incubation with S9 enzymes. The chromatographic and spectroscopic properties of this metabolite suggest it is a hydroxylated derivative of 1NP. It exhibits a high mutagenicity with TA98 and TA98NR but is markedly less active towards the dinitropyrene-resistant strains. There is no evidence to suggest that the S9-dependent activation of 6NBaP involves bacterial nitroreductase activity. This compound may be activated entirely by S9 enzyme activity to form a reactive product such as an epoxide. Thus, the increased mutagenicity of a nitro-PAH compound in the Salmonella/S9 assay may be either dependent or independent of bacterial nitroreductase activities. (no Refs)

31. RAT LIVER MICROSOMAL METABOLITES OF 7-METHYLBENZ[C]ACRIDINE.

Ireland CM, Cheung HT, Ryan AJ, Holder GM
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Chem Biol Interact; 40(3):305-318 1982

The metabolism of the weak carcinogen 7-methylbenz[c]acridine (7MBAC) was examined in rat liver microsomes from 3-methylcholanthrene (MC)-induced animals by the use of mixed 14C- and 2H-labeled substrate. The three metabolites identified by spectroscopic and chromatographic examination were 7-OHMBAC and two dihydrodiols. The dihydrodiols were assigned structures consistent with attack on the 8,9-and 5,6 or K-region of the aromatic system. (Author abstract) (32 Refs)

32. METABOLISM OF 7H-DIBENZO(C,G)CARBAZOLE IN SPRAGUE-DAWLEY RAT LIVER MICROSOMES (MEETING ABSTRACT).

Warshawsky D, Myers BL, Dooley J, Schoeny R, Christian R
Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH, 45267
Proc Am Assoc Cancer Res; 23:320 1982

The metabolism and mutagenicity of 7H-dibenzo(c,g)carbazole (DBC) is under investigation in our laboratory. Incubation of DBC with liver microsomes prepared from 3-methylcholanthrene-treated (3MC) rats resulted in the production of nine metabolites separable by HPLC (high pressure liquid chromatography) and characterized by spectroscopic techniques. Further identification of the metabolites and delineation of the metabolic pathways of DBC were accomplished by incubation of DBC and enzyme inhibitors/ activators (styrene oxide, trichloropropene oxide, cyclohexene oxide, glycidol or SKF525A) with rat liver microsomes followed by HPLC. Metabolites 1 and 2 were identified as dihydrodiols while metabolites 3 through 5 were identified as phenols. DBC was found to be mutagenic for a Chinese hamster epithelial line DPI 3, when cocultivated with Syrian hamster embryo (SHE) cells using 6 thioguanine for selection. Results of Salmonella/microsomal reverse mutation assays were equivocal for DBC. Forward assays to 8-azaguanine resistance using Salmonella strain TM677 showed DBC to be nonmutagenic. When assayed in DPI 3/SHE system metabolites 5, 7, and 8 were mutagenic. In the forward mutation assay the mutagenicity of DBC metabolites was dependent upon the activation system; without S9, metabolite 2 was positive; 3MC S9, 10 metabolites were positive; Aroclor 1254 S9, 3b was mutagenic. (no Refs)

BINDING TO CELLULAR MACROMOLECULES

33. THE ROLE OF CARRIER PROTEINS IN THE OXIDATION OF BENZO(A)PYRENE IN RAT LIVER (MEETING ABSTRACT).

Hanson-Painton O, Griffin MJ, Tang JN
Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104
Fed Proc; 41(3):927 1982

Cytosolic proteins possess the ability to serve as carrier between particulate benzo(a)pyrene (BP) and the microsomal cytochrome P450. The carrier mechanism of the partially purified 46,000-dalton protein (C) was investigated. Using [14C] BP and Sephadex G-100 chromatography, we have demonstrated that (1) the transfer of BP from C to microsomes (M) is predominately in the forward direction, (2) C is capable of recycling between BP and M, (3) BP in isolated BP-M can be oxidized by the addition of NADPH, (4) the oxidized BP (BP*) in M can then be transferred to fresh C in the forward direction, and (5) BP* in M will not dissociate from M without the presence of C. The presence of BP and BP* in various fractions has been shown by HPLC (high pressure liquid chromatography). Thus C can be a carrier for both BP and BP*. The direction of transfer is the same as expected for metabolism of BP in vivo, suggesting that C has such an in vivo role. (no Refs)

34. THE PRESENCE OF CARRIER FOR ACTIVATED BENZO[A]PYRENE METABOLITE IN HUMAN AND MOUSE CELLS (MEETING ABSTRACT).

Lo KY, Kakunaga T, Yamamoto S
National Cancer Institute, National Institute of Health, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:245 1982

It has long been an unsolved question how the ultimate form of benzo[a]pyrene, (+/-)7 beta,8 alpha-dihydroxy-9 alpha,10 alpha epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDEI) reaches nuclear DNA in spite of the study of its instability in aqueous solution. The object of this study is to determine the fate of BPDEI in cells, and clarify its biological implication. In normal diploid human fibroblasts and mouse A31-1-1 cells treated with BPDEI (0.33-3.3uM), the removal of BPDEI-DNA adducts showed a biphasic kinetics-a rapid removal phase followed by a slow removal phase. Removal of BPDEI adducts in the repair-deficient Xeroderma pigmentosum cells (XP12BE and 1261) under the same conditions gave biphasic kinetics also--a fast removal phase followed by a plateau phase. These findings suggest the possibility that the rapid removal of DNA adducts in the first phase reflects the decline of amounts of BPDEI which remains chemically active in cells for a few hours, and interact with DNA upon cell lysis. Plasmid PBR322 DNA was added to the lysates of the BPEDI-treated cells, and BPDEI bound to plasmid DNA was measured. The amount of BPDEI-DNA adduct formed in the plasmid DNA decreased, in parallel with those in host DNA, with time of post-incubation. The cell components which stabilize or carry BPDEI were searched in fractionated cell lysates by using this method. It was found that microsomal fraction had the ability to transfer BPDEI to DNA, however partially purified P450 could not. (no Refs)

35. TRANSPORT OF PHYSIOLOGICAL CONCENTRATIONS OF BENZO(A)PYRENE INTO HUMAN CELLS VIA A LIPOPROTEIN CARRIER (MEETING ABSTRACT).

Busbee DL, Rankin PW
Department of Biological Sciences, North Texas State University Genetics Center, Denton, TX, 76203
Proc Am Assoc Cancer Res; 23:410 1982

Human serum lipoproteins were purified by size exclusion HPLC (high pressure liquid chromatography). Column effluent fractions were quantitated for capacity to bind [3H] benzo(a)pyrene; binding was correlated with lipoprotein-cholesterol levels in the fractions. Efficiency of binding of benzo(a)pyrene to lipoproteins correlated directly to lipoprotein concentrations, and not to carcinogen concentration. Low density lipoproteins potentiated transfer of non-covalently bound [3H]-7,8-dihydrodiol-9,10-epoxybenzo(a)pyrene into non-mitogen-stimulated human lymphocytes held in vitro in RPMI 1640 for 24 hours without serum to deplete lipoproteins bound to the cell membrane. At high concentrations carcinogen entered the cells and was bound to lymphocyte DNA in the absence of low density lipoprotein, and without relation to time of exposure of the cell to carcinogen. When carcinogen at very low concentrations 10 ng/ml, was introduced to cells non-covalently bound to low density lipoprotein, carcinogen binding to DNA increased as a function of time. Exposure to 10-fold increased concentrations of carcinogen in the absence of low density lipoprotein did not result in carcinogen bound to DNA. Adsorptive endocytosis of lipoproteins carrying non-covalently associated carcinogens represents a potential mechanism for intracellular transport of carcinogens available at physiological concentrations. (no Refs)

36. BENZO(A)PYRENE (BP) BINDING TO CYTOSOLIC PROTEIN ENHANCES ITS MICROSOMAL OXIDATION (MEETING ABSTRACT).

Dixit R, Bickers DR, Mukhtar H
Department of Dermatology, Veterans Administration Medical Center and Case Western Reserve, University Cleveland, OH, 44106
Fed Proc; 41(3):1730 1982

It is possible that certain cytosolic proteins with adequate binding sites may facilitate the transport of lipophilic carcinogens such as BP to the site of mixed function oxidase action. Sephadex G-100 gel permeation chromatography of rat liver cytosol saturated with 14C-BP resulted in two peaks of protein bound radioactivity. Glutathione-S-transferase (GST) activity (with 1 chloro 2,4 dinitrobenzene and BP-4,5-oxide as substrates) was eluted as a single major peak which coincided with one peak of protein bound BP by microsomes from control or 3-methylcholanthrene pretreated rats was significantly enhanced as compared to ethanol suspended BP. This enhanced formation was not a protein effect since oxidized product formation in the presence of bovine serum albumin or heat denatured protein was not different from that of ethanol-suspended BP. The formation of oxidized products from protein bound BP was time and microsomal protein concentration dependent, required NADPH and was inhibited by the monooxygenase inhibitors alpha -napthoflavone, metyrapone, SKF-525A and 1-benzylimidazole. These results indicate that the presence of soluble proteins in rat liver cytosol having an affinity with BP would facilitate its microsomal tranport from one segment of endoplasmic reticulum to another which allows better microsomal utilization of BP. Coemergence of BP binding protein with GST suggests that the soluble protein could be one of the glutathione S-transferases such as ligandin. (no Refs)

37. HORSERADISH PEROXIDASE/HYDROGEN PEROXIDE (HRP/H2O(2)) BINDING OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH) BY ONE-ELECTRON OXIDATION (MEETING ABSTRACT).

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Eppley Institute for Research in Cancer, University of Nebraska Medical, Center Omaha, NE, 68105
Proc Am Assoc Cancer Res; 23:239 1982

Several lines of evidence indicate that HRP/H2O2 catalyzes binding of PAH by one-electron oxidation. However, proof lies in elucidating adducts obtained between PAH and biologic macromolecules. The carcinogenic 6-methylbenzo[a]pyrene (BP-6-CH(3)), in which activation by one-electron oxidation occurs at the 6-methy group, was accordingly used. Calf thymus DNA (1 mg/ml), HRP (Type II, 0.1 mg/ml), 5 X 10-4M H2O2 and 70 uM [14C]BP-6-CH3 were incubated in 0.067 M Sorenson buffer, pH 7, for 1 hr at 37 C. After purification DNA (1 mg/ml) in 0.05 M Bis-Tris, 5 mM MgCl2, pH 7.1 was incubated with 0.1 mg/ml deoxyribonuclease I for 3 hr at 37 C under argon. The mixture, partially saturated with (NH(4))2SO4, was extracted 3 times with n-butanol. The residue, after evaporation of n-butanol, was analyzed by reverse-phase high performance liquid chromatography and its profile was compared to that from the hydrolyzed BP-6-CH2BR and DNA. Only a major adduct was present in the HRP/H2O(2)-activated system and the same adduct was also in the BP-6-CH2BR-DNA system. Both collected adducts co-chromatographed in 3 additional elution systems with the adduct obtained from deoxyguanosine (dG) and BP-6-CH2Br. Nuclear magnetic resonance spectra of the synthetic adduct showed that BP-6-CH3 binds through the methyl group to the 2-amino group of dG. Thus, structure elucidation of the HRP-H2O(2)-catalyzed adduct between BP 6-CH3 radical cation is the reactive intermediate responsible for the binding and HRP/H2O2 activation occurs by one-electron oxidation. (1 Ref)

38. DEFECTIVE BINDING OF 3-METHYLCHOLANTHRENE TO THE AH RECEPTOR IN C3H/10T1/2 CELLS (MEETING ABSTRACT).

Okey AB, Mason ME, Gehly EB, Heidelberger C, Muncan J, Dufresne MJ
Division of Clinical Pharmacology, Hospital for Sick Children, Toronto, Ontario, M5G 1X8, Canada
Proc Am Assoc Cancer Res; 23:315 1982

The initial step in induction of aryl hydrocarbon hydroxylase (AHH; cytochrome P1-450) is binding of polycyclic aromatic inducers such as 3-methylcholanthrene (MC) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to a specific cytosol protein, the Ah receptor. The inducer:receptor complex then translocates from cytoplasm into the nucleus where it somehow stimulates production of specific messenger (m)RNAs. C3H/10T1/2 cells exhibit AHH induction when treated with benzo(a)pyrene (BP) or benz(a)anthracene (BA), but are competely unresponsive to AHH induction by MC. Cytosolic and nuclear forms of the Ah receptor can be detected in 10T1/2 cells using [3H] TCDD as the radioligand, but direct binding of [3H]MC to Ah receptor is not detectable in 10T1/2 cells. In contrast, in Hepa-1 cells which exhibit AHH induction when treated with MC, TCDD, BA or BP, cytosolic and nuclear Ah receptor can be detected either with [3H]MC or [3H]TCDD. Nonradioactive MC retains its ability to compete with [3H]TCDD for Ah receptor in the 10T1/2 cells, but the relative potency of MC as a competitor in 10T1/2 cells is less than that in Hepa-1 cells or in rodent liver. It appears that the inability of 10T1/2 cells to exhibit AHH induction when treated with MC (while retaining responsiveness to BP and BA) is due to defective interaction of MC with the Ah receptor. (1 Ref)

39. COMPARISON OF LEVELS OF BENZO(A)PYRENE-7,8-DIOL-9,10-EPOXIDE (BPDE) DIASTEREOMERS AND ENANTIOMERS COVALENTLY BOUND IN VIVO TO MACROMOLECULAR COMPONENTS OF WHOLE EPIDERMIS VERSUS THE BASAL CELL LAYER (MEETING ABSTRACT).

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Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:246 1982

The binding of anti-BPDE, the ultimate carcinogenic metabolite of benzo(a)pyrene, and its noncarcinogenic syn-diastereomer was investigated in mouse epidermis in vivo. Sencar mice were exposed for various times to topically applied (+)anti and (+)syn diastereomers of BPDE and the levels of BPDE bound to cell macromolecules were determined. A comparison of the amounts of (+)anti and (+)syn-BPDE bound to RNA, DNA, and protein isolated from whole epidermis indicated that a differential binding pattern had occurred, with 2x more (+)anti-than (+)syn-BPDE present in DNA after 24 hours. In contrast, no significant difference in levels of (−)anti and (+)syn adducts was observed in macromolecules isolated from purified basal cells, the presumed target cell population for initiation. Additional binding studies with the optically pure (+) and (-) enantiomers of BPDE-anti indicated a significant difference in levels of adducts formed, with 2-3x more (+) anti- than (-) anti-BPDE bound to DNA purified from the basal cell layer. The higher level of binding by (+)anti-BPDE to DNA of basal cells reflects the previously demonstrated relative tumorigenic activities of these two enantiomers. (no Refs)

40. METABOLIC ACTIVATION OF AFLATOXIN B1 AND BENZO(A)PYRENE IN EXPLANT CULTURES OF HUMAN TISSUE (MEETING ABSTRACT).

Grafstrom RC, Autrup H, Trump BF, Harris CC
National Cancer Institute, Bethesda, MD, 20205
Fed Proc; 41(3):330 1982

Binding of aflatoxin B1 (AFB) and benzo(a)pyrene (BP) to DNA was compared in non-tumorous human bronchial (HB), esophageal (HE), colonic (HC), and duodenal (HD) tissues obtained at the time of either surgery or autopsy. Tissues were incubated for 24 hr with radiolabelled AFB or BP at 1.5 M in a chemically defined medium. The binding level of the carcinogen to epithelial DNA varied widely among tissues and individuals. Binding levels of AFB (pmol carcinogen bound to 10 ng DNA) were as follows: HE (mean 16, range 0-92, cases 28); HE (11, 0-35, 11); HC (8, 0-44, 27); and HD (23, 0-46, 11). Binding levels of BP were: HB (25, 0-160, 26), HE (27, 0-104 11), HC (8, 0-44, 24); and HD (21, 0-58, 10). Thus, the order of mean binding values among the tissues was for AFB: HD greater than HB greater than HE greater than HC, and for BP HE greater than HB greater than HD greater than HC. In tissues where the metabolism of both carcinogens was studied, binding of BP was generally higher than that of AFB. Analysis revealed no correlation between binding levels of the two carcinogens in any of the tissue types. The results indicate quantitative differences in carcinogen activation among tissues and demonstrate the variation in carcinogen metabolism among individuals. (no Refs)

41. METABOLISM OF BENZO(A)PYRENE AND AFLATOXIN B1 IN CULTURED HUMAN AND ANIMAL MODEL BLADDER AND TRACHEOBRONCHIAL TISSUES (MEETING ABSTRACT).

Daniel FB, Stoner GD, Sandwisch PW, Schenck KM, Schut HA
Health Effects Research Laboratory, U.S Environmental Protection Agency, Cincinnati, OH, 45268
Proc Am Assoc Cancer Res; 23:327 1982

The metabolism, DNA binding and -adduct formation of benzo(a)pyrene (BP) and aflatoxin B1 (AFB) in human and animal species (monkey, rat, hamster, dog) has been compared using cultured explants of bladder and tracheobronchial tissues. Human bladder and bronchial specimens obtained from autopsies and animal tissues obtained from sacrifice were cultured as explants in serum-free medium. The cultures were rocked to permit intermittent tissue exposure to medium and atmosphere. After three days, the explants were exposed for 24 hrs to either [3H]BP or [3H]AFB (10-6M each). Epithelial cell DNA was isolated by hydroxyapatite chromatography and, after hydrolysis of the DNA, high pressure liquid chromatography (HPLC) was used to identify the carcinogen-DNA adducts. Among the species, BP binding to bladder cell DNA was highest in the human and lowest in the rat and that to tracheobronchial DNA was highest in the hamster and lowest in the dog. For both bladder and tracheobronchial tissues, AFB binding to DNA was highest in the hamster and lowest in the human. In all tissues, 2,3-dihydro-2-(N7-guanyl)-3-hydroxy-AFB and 7,8,9-trihydroxy-10(-N2-deoxyguanosine)-bP adducts were identified after incubation with AFB and BP, respectively. The profile of BP metabolites in the medium (analyzed by HPLC) from all tissues was qualitatively similar. (no Refs)

42. DOSE-RESPONSE FOR BENZO(A)PYRENE METABOLITE-DNA ADDUCTS IN LUNG, LIVER, AND FORESTOMACH OF MICE (MEETING ABSTRACT).

Anderson MW, White CM, Adriaenssens PI
National Institute of Environmental Health Science, Research Triangle Park, NC, 27709
Fed Proc; 41(3):1548 1982

The formation of benzo(a)pyrene (BP) metabolite-DNA adducts in lung, liver, and forestomach of female A/HeJ mice was examined as a function of BP dose (po) ranging from 2 to 1350 umol/kg. The major identified adduct in each tissue at each dose was the 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydro-BP (BPDEI)-deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydro-BP(BPDEII)-deoxy guanosine adduct and a BP-phenol-oxide-DNA adduct were also observed. The dose-response curves for these adducts were sigmoidal in each tissue. The DNA binding expressed as percentage of exposure dose was largest at a BP dose of 0.3 mmol/kg. The dose-response relationships approached linearity at low doses. Thus, the results of these dose-response studies do not reveal the existence of any threshold dose below which binding of BP metabolites to DNA does not occur. Dose-response curves for binding of BP metabolites to protein were also investigated. The ratio of BPDE-DNA adduct levels to protein binding levels was non-linearly related to exposure dose. Thus, binding of BP metabolites to protein cannot be used as a gauge of BP metabolite-DNA binding. These and similar dose-response relationships for polycyclic aromatic hydrocarbons (PAH) metabolite-DNA adducts should be helpful in the low dose extrapolation problem for PAH carcinogenesis. (no Refs)

43. FORMATION OF A 7-HYDROXYMETHYL-12-METHYLBENZ[A]ANTHRACENE-DNA ADDUCT FROM DMBA IN MOUSE EPIDERMIS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:244 1982

The present study was designed to investigate the role of 7-hydroxymethyl-12-methylbenz(a)anthracene (7-OHM-12-MBA) in the covalent binding of DMBA (dimethylbenzanthracene) to mouse epidermal DNA. The covalent binding of [3H]7-OHM-12-MBA to mouse epidermal DNA was compared with [3H]DMBA. Twenty-four hours after application of [3H]7-OHM-12-MBA (400 nmol) or [3H]DMBA (10 nmol) to the skins of SENCAR mice, the covalent binding was 23.0 or 4.5 pmol/mg epidermal DNA, respectively. The isolated DNA samples were hydrolyzed to deoxyribonucleosides and chromatographed on Sephadex LH20 columns. With DMBA, four distinct DMBA-DNA adduct peaks eluted after the p-(nitrobenzyl)-pyridine (p-NBP) marker. A fifth, early eluting peak, cochromatographed with p-NBP marker. When [3H]7-OHM-12-MBA was applied to the skins of mice, three distinct DNA-adduct peaks were observed. The major 7-OHM-12-MBA-DNA adduct eluted with the p-NBP marker and cochromatographed on high performance liquid chromatography with the early eluting DMBA-DNA adduct. The other 7-OHM-12-MBA-DNA adducts did not cochromatograph with any DMBA-DNA adducts. Interestingly, benzo[e]pyrene, which markedly inhibited DMBA tumor-initiation and DNA-adduct formation in SENCAR mice, had no effect on DNA-adduct formation with 7-OHM-12-MBA. The results suggest that a hydroxymethyl-metabolite gives rise to a minor DMBA-DNA adduct in mouse skin and that 7-OHM-12-MBA, when applied topically, may be processed by epidermal cells in a manner different from that of DMBA. (2 Refs)

44. RELATIONSHIP OF POLYCYCLIC HYDROCARBON (PH) METABOLISM IN RAT MAMMARY CELLS TO TUMOR SUSCEPTIBILITY IN VIVO (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:318 1982

Since tumor induction rates by PHs vary widely among rat strains, we have confirmed the high susceptibility of Sprague-Dawley (SD) rats to mammary tumorigenesis by 7,12-dimethylbenz(a)anthracene (DMBA) compared to the Long-Evans (LE) strain. We have also found a similar difference between two inbred rat strains, Wistar-Furth (W/Fu) and F344, respectively. Using cultured mammary cells, divided into epithelial or stromal enriched populations from these 4 strains, we examined DMBA and benzo(a)pyrene (B(a)P) metabolism in relation to in vivo differences in tumor induction rates. B(a)P was converted to water-soluble metabolites at significantly higher rates than DMBA, with a constant ratio of metabolism of the two PHs, in all cell systems tested. The stromal cell populations, which are less susceptible to carcinogenesis in vivo, converted B(a)P and DMBA to water-soluble metabolites 2-4 times faster than the epithelial cell cultures. In contrast, cells from the high susceptibility strains, SD and W/Fu, showed higher levels of water-soluble metabolite production than the less susceptible strains. High-pressure liquid chromatographic analysis of ethyl acetate-extractable B(a)P metabolites formed in both mammary cell populations from all 4 strains revealed predominantly 9,10-and some 7,8-dihydrodiol formation,

but no major differences by cell type or rat strain. We have measured activation of DMBA and B(a)P to mutagenic metabolites by mammary cells from SD and LE rats, and found similar rates in both strains. (no Refs)

45. A PROBABLE MECHANISM FOR SYNERGISTIC EFFECT IN CHRYSOTILE AND BAP INDUCED TRANSFORMATION (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:199 1982

It is generally believed that the initial step of chemically induced cellular transformation is the fixation of DNA damage(s). Using a normal human skin fibroblast cell culture system, we investigated: 1) the cytotoxic effect of chrysotile asbestos; 2) thymidine incorporation, and 3) cellular uptake of BaP (benzo(a)pyrene) under the influence of asbestos. We observed: 1) chrysotile asbestos (10 ug/ml) exerted cytotoxicity at a cell density below confluency; 2) chrysotile treatment enhanced thymidine incorporation from the first to the fourth day post-treatment both in the presence or absence of BaP; 3) BaP uptake was enhanced in the culture simultaneously treated with asbestos. The preliminary findings indicate that protein and RNA binding of BaP was enhanced in the presence of chrysotile asbestos. Based on the data collected, we suggest that in the event of co-exposure of chrysotile asbestos and BaP, more DNA damage will result, that thymidine incorporation will be enhanced and is indicative of increased levels of DNA replication thereby leading to the fixation of genetic damage. (no Refs)

46. THE INFLUENCE OF ASBESTOS ON THE FORMATION AND REMOVAL OF BENZO(A)PYRENE-DNA ADDUCTS IN A HAMSTER TRACHEAL EPITHELIAL CELL LINE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:236 1982

The effect of asbestos fibers (crocidolite and chrysotile) on the interaction of benzo(a)pyrene (BP) with a hamster tracheal epithelial cell line (HTE-B) has been investigated. When BP alone was incubated with HTE-B cells, 50% of the applied hydrocarbon was recovered as water soluble metabolites at 8 hr while 5% was recovered as intracellular unmetabolized BP. After 8 hr incubation with BP, the medium was replaced and a 50% reduction in alkylation was observed in 24 hr with about 80% removed by 5 days. High performance liquid chromatography separation of the DNA adducts demonstrated six adducts. Of these six adducts, two were rapidly removed while two were relatively poorly removed during the 5 day repair period. In comparative studies, BP was coated onto asbestos and applied to HTE-B cells. An enhanced uptake was observed with 80% BP associated with the cells after 1 hr. Metabolism was only slightly inhibited as compared to experiments without asbestos but at 8 hr nearly 50% of the applied hydrocarbon was retained by the cells in unmetabolized form. Analysis of repair was complicated by continued formation of alkylated products in DNA after removal of BP. However, after 24 hr post-treatment, only 5% of the applied BP remained in the cells. At 5 days, it appeared that removal of DNA-bound adducts was inhibited. Experiments with both crocidolite and chrysotile gave the same results. It is concluded that the cocarcinogenic effect of asbestos may be due to enhanced cellular uptake of BP as well as inhibition of subsequent DNA repair. (no Refs)

47. EFFECT OF BUTYLATED HYDROXYANISOLE (BHA) ON DOSE-RESPONSE FOR BENZO(A)PYRENE (BP) METABOLITE-DNA ADDUCTS IN MICE (MEETING ABSTRACT).

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National Institute of Environmental Health Science, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:355 1982

The phenolic antioxidant, BHA, has been shown to be a potent inhibitor of the neoplastic effects of BP in mouse lung and forestomach. We previously showed that BHA treatment of mice inhibited BP metabolite-DNA adduct formation in the lung to the same degree that BP-induced pulmonary adenoma formation was inhibited. In this study the formation of BP metabolite-DNA adducts in lung, liver, and forestomach of control and BHA-treated female A/HeJ mice was examined as a function of BP dose (po) ranging from 2 to 1350 umol/kg. The major identified adduct in each tissue at each dose was the 7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydro-BP (BPDEI)-deoxyguanosine adduct. The 7beta,8alpha-dihydroxy-9beta, 10beta-epoxy-7,8,9,10-tetrahydro-BP (BPDEII)-deoxyguanosine adduct and a BP-phenol-oxide-DNA adduct were also observed. In untreated animals the dose-response curves for these adducts were sigmoidal in each tissue. In forestomach the dose-response curve for BPDE-DNA adducts levels in BHA-treated mice was parallel to the curve for control animals and, thus, the inhibition (45%) of adduct formation was independent of BP dose. In contrast, BHA treatment diminished the curvilinear nature of the dose-response curves for BPDE adducts in lung and live. The dose-response curves in lung and liver of treated animals were approximately linear. The inhibition in lung (70%) and liver (80%) was highest at a BP dose of 0.3 mmol/kg. As BP dose approached zero, the inhibition of BPDE-DNA adduct formation decreased with BP dose and approached values of 40% (lung) and 55% (liver). (1 Ref)

48. IN VIVO PROTECTION BY INDOLE-3-CARBINOL AGAINST CARCINOGEN COVALENT BINDING TO MOUSE HEPATIC MACROMOLECULES (MEETING ABSTRACT).

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Fed Proc; 41(3):1559 1982

Indole-3-carbinol (I3C) is a normal constituent of the human diet and is contained in such cruciferous vegetables as cabbage, broccoli, brussels sprouts and cauliflower. When ingested by rodents, this compound has been shown to induce aryl hydrocarbon hydroxylase activity and to confer some protection against polynuclear aromatic hydrocarbon induced neoplasia. We examined the pattern of microsomal enzyme induction in mice gavaged with I3C in corn oil. Hepatic cytochrome P-450, aryl hydrocarbon hydroxylase, and ethoxyresorufin deethylase reached maximum levels in about 5 days. These and other data suggest that the form of cytochrome P-450 induced by I3C is similar to that produced by aryl hydrocarbons. When mice were gavaged with I3C, followed by gavage with 14C-N-nitrosodimethylamine (NDMA) or 14C benzo(a)pyrene (BaP), there resulted a large decrease in the total amount of radioactivity covalently bound to hepatic macromolecules, when compared with corn oil gavaged controls. This decrease in covalent binding was evident in nuclear, mitochondrial, microsomal and supernatant subcellular fractions, as well as in DNA, RNA and protein in each subcellular fraction where they occur. The

decrease in binding of NDMA and BaP metabolites occurred within 1 hr after I3C administration, and therefore appeared to have no relationship to the microsomal enzyme induction discussed above. (no Refs)

MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

49. HISTOCHEMICAL LOCALIZATION OF GAMMA-GLUTAMYL-TRANSPEPTIDASE AND CONCANAVALIN A IN NORMAL, PRENEOPLASTIC, AND NEOPLASTIC EPITHELIA (MEETING ABSTRACT).

Klein-Szanto AJ, Shiba M, Shah Y, Slaga TJ
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71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Gamma-Glutamyltranspeptidase (GGT) was studied histochemically in several murine epidermal lesions produced in the course of a two-stage carcinogenesis protocol using DMBA (dimethylbenzanthracene) and TPA (12-O-tetradecanoyl phorbol 13-acetate). GGT was absent in both normal and hyperplastic epidermis. Approximately 30 per cent of papillomas exhibited small GGT-positive areas. This percentage increased to approx 60 per cent when whole mounts of papillomas (instead of sections) were used. All squamous carcinomas showed GGT-positive areas. GGT localization was also studied in several lesions produced by DMBA in rat trancheal transplants. Although normal mucociliary epithelia exhibited some enzyme activity, more intense staining was seen in the hyperplastic epithelia. Squamous metaplasia without atypia showed decreased GGT activity, whereas in dysplastic and neoplastic epithelia, marked GGT staining was noted. Fluorescein-labeled concanavalin A localization was also studied in these tissues. Hyperplastic epithelium showed the highest affinity, whereas normal epithelium exhibited less fluorescence. Metaplastic, dysplastic and neoplastic epithelia from the respiratory tract showed less affinity to the lectin than normal epithelium. A similar pattern was observed in a restricted number of preneoplastic lesions of the human bronchi. Lectin binding to normal skin and cutaneous lesions did not reveal any significant differences. (no Refs)

50. INVESTIGATION OF THE CARCINOGEN-SPECIFIC NATURE OF GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT)-RICH CELLS CHEMICALLY INDUCED IN HAMSTER BUCCAL POUCH EPITHELIUM (HBPE) (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:211 1982

This study was undertaken to determine whether the chemical induction of GGT stained cells in HBPE is carcinogen-specific and thus likely to be a relevant event in HBPE carcinogenesis. Three known carcinogens and several non-carcinogenic irritants were applied repeatedly over a period of several weeks to the buccal pouches of male syrian hamsters. An attempt was made to maximize the exposure of the mucosa to the various agents without destroying the epithelium. At various intervals whole mounts were prepared for histochemical detection of GGT staining basal cells. Full thickness whole mounts of several sq cm in surface area could be harvested from each animal. Multiple discrete populations of GGT stained cells were detected in whole mounts of HBPE exposed to the potent carcinogens 7-12-dimethylbenz(a)anthracene, N-methyl-N-benzylnitrosamine and N-methyl-N-nitrosourea. GGT stained cells were not detected in whole mounts of HBPE exposed to topical applications of croton oil, 12-O-tetradecanoylphorbol-13-acetate (in acetone, 100 ug per application), acetic acid (25% aq sol), ethylphenylpropiolate (6.6% in acetone), phenol (5% in ethylene glycol), retinol palmitate (10% in oil) or turpentine (50% in oil). These results suggest that the induction of GGT stained cell populations may be a significant event in HBPE carcinogenesis rather than a trivial consequence of cellular toxicity or non-specific irritation. (no Refs)

51. INCREASED URIDINE DIPHOSPHATE-GLUCURONYLTRANSFERASE ACTIVITY IN PRENEOPLASTIC LIVER NODULES AND MORRIS HEPATOMAS.

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Cancer Res; 42(9):3747-3752 1982

In preneoplastic rat liver nodules produced by 2-acetylaminofluorene, certain uridine diphosphate-glucuronyltransferase (UDP-GT) activities, which are ascribed to a distinct enzyme form, were selectively increased (5-fold). This enzyme form, operationally termed UDP-GT1, accepts 1-naphthol,4-methylumbelliferone, and 3-hydroxybenzo(a)pyrene as substrates and is chiefly inducible in liver by 3-methylcholanthrene-type inducers. Glucuronidation of other substrates (morphine, 4-hydroxybiphenyl, chloramphenicol, bilirubin, and estrone) was only slightly enhanced or decreased in nodular tissue. Differentially increased UDP-GT1 activities were also found in Morris hepatomas 9121 and 7777. Rabbit antibodies to rat liver UDP-GT1, purified from 3-methylcholanthrene-treated rats, demonstrated immunological similarity between the enzymes from liver, nodular tissue, and Morris hepatoma 9121. Rocket immunoelectrophoresis ascertained that enhanced enzyme activity in nodular tissue reflected an increased level of enzyme protein. Increased activity of UDP-GT1 together with decreased cytochrome P-450-dependent monooxygenase may contribute to the resistance of preneoplastic hepatocytes to the cytotoxic actions of chemical carcinogens. (Author abstract) (43 Refs)

52. THE INDUCTION OF THE D-T DIAPHORASE AND THE NAD(P)H-NITRO BT REDUCTASE BY CARCINOGENIC POLYCYCLIC HYDROCARBONS IN THE SPLEEN AND LYMPH NODES OF THE RAT (MEETING ABSTRACT).

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Fed Proc; 41(3):330 1982

The polycyclic hydrocarbons 3,4-benzpyrene, 7,12-dimethylbenzanthracene and 3-methyl cholanthrene induce the activity of the soluble enzyme D-T diaphorase in rat spleen and lymph nodes. The dehydrogenation of NAD(P)H in fractions sedimented at 8000 and 100000 g in the same animals is not affected by the treatment. The induction of the soluble diaphorase is dose dependent and is inhibited by dicumarol. The histochemi-

cal activity of the NAD(P)H-NBT reductase is also induced by carcinogens, this enzyme is localized in histiocytes and T lymphocytes; B lymphocytes, even after the administration of carcinogens, show a very weak activity. The staining of the NAD(P)H-NBT reductase is not specific for the D-T diaphorase but the negative effects of the carcinogens on the particulate enzymes suggest the observed increase in histochemical activity may be due to the D-T diaphorase. These results seem to indicate that a) lymphoid organs participate actively in the metabolism of carcinogens, b) this function may be specific for histiocytes and T lymphocytes, and c) the inductive histochemical and biochemical action of carcinogens may be another useful and reliable parameter to differentiate B and T lymphocytes in experimental animals. (no Refs)

53. THE EFFECTS OF RIBOFLAVIN DEPLETION AND 3-METHYLCHOLANTHRENE TREATMENT ON HEPATIC AZOREDUCTASE AND D.T. DIAPHORASE (MEETING ABSTRACT).

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Fed Proc; 41(3):357 1982

Hepatic azoreductase and DT diaphorase are involved in the metabolism of xenobiotics and carcinogens. Both enzymes are flavoproteins and induced by 3 methylcholanthrene (3MCA). The effect of riboflavin deficiency on hepatic levels of these enzymes and their inductions by 3MCA was examined in male Sprague-Dawley rats fed a deficient diet for 6 weeks. Controls received deficient diet supplemented with riboflavin in the drinking water (20 ug/ml). 3MCA was injected ip daily for three days prior to sacrifice (10 mg/kg). Both enzymes were predominantly located in the cytosol where riboflavin deficiency resulted in a 41.9% decrease in azoreductase and a 59.6% decrease in diaphorase. Microsomal diaphorase and azoreductase were only slightly decreased. 3MCA resulted in a 10 and 14 fold increase in cytosolic azoreductase and diaphorase in controls, whereas deficient rats elicited a 13 and 20 fold increase in the activity of these enzymes. Both cytosolic enzymes were inhibited 60% by Warfarin in control rats. Warfarin inhibition increased to greater than 90% in cytosols from 3MCA treated rats. Microsomal azoreductase and DT diaphorase were increased 4 and 2 fold respectively by 3MCA. These results indicate that riboflavin deficiency does not inhibit the induction of azoreductase and diaphorase by 3MCA. (no Refs)

54. 3-METHYLCHOLANTHRENE INDUCES PHENOBARBITAL-INDUCED CYTOCHROME P-450 HEMOPROTEIN IN FETAL LIVER AND NOT CYTOCHROME P-448 HEMOPROTEIN INDUCED IN MATERNAL LIVER OF RATS.

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Biochem Biophys Res Commun; 107(1):6-11 1982

Absorption characteristics of drug-metabolizing enzymes in fetal rat liver following various induction regimens was investigated. The aminopyrene (AM) and hexobarbital (HB)-metabolizing activities of fetal liver microsomes on day 21 of pregnancy were induced by 3-methylcholanthrene (3MC) administered on day 18 and 19 of pregnancy. No inductive effect was observed in the maternal microsomes. These results suggested that the inductions of the AM- and HB-metabolizing activities occurred only during the fetal period. No inductive effect of 3MC on AM- and HB-metabolizing activities was observed in newborn liver microsomes following fetal administration of 3MC. The disappearance of 3MC inducing effects at birth suggested that a hemoprotein different from that induced in maternal liver microsomes was induced in fetal liver microsomes by maternal administration of 3MC. Maximum carbon monoxide difference spectra of cytochrome P-450 from 3MC-pretreated maternal liver yielded a peak at 448 nanometer (nm), compared to 450 nm for fetal liver microsomes. The hemoprotein induced in fetal liver by 3MC appeared to be the same as that induced in maternal liver by phenobarbital. (16 Refs)

55. PULMONARY CYTOCHROMES P-450 FROM RABBITS TREATED WITH 3 METHYLCHOLANTHRENE.

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Mol Pharmacol; 20(1):221-228 1982

The effects of pretreatment of rabbits with 3-methylcholanthrene (3-MC, 25 mg/kg/day for 4 days) on the catalytic and spectral properties of lung microsomes were studied, and the chromatographic, spectral and electrophoretic properties of partially purified pulmonary cytochromes P-450 were compared in 3-MC-treated and untreated rabbits. Treatment with 3-MC caused a 2-fold induction of benzo[a]pyrene hydroxylase activity, but had no effect on ethylmorphine N-demethylase activity. Column chromatographic peaks of two microsomal cytochromes, P-450I and P-450II, were qualitatively and quantitatively similar from both untreated and 3-MC-treated rabbits, but a third peak (cytochrome P-450III) was found only in preparations from treated animals. Both ethyl isocyanide and CO-difference spectral determinations clearly showed that cytochrome P-450III differed from the other two cytochromes. The in vitro stabilities of P-450I and P-450III were similar, and much less than that of P-450II. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of purified cytochromes P-450 from rabbit lung confirmed the presence of P-450I and P-450II in samples from both untreated and treated animals, and in addition showed a 58,000 mol wt protein associated with the induction of P-450III by 3-MC. P-450I and P-450III are both less stable than P-450II in retaining heme-associated peroxidase activity. (39 Refs)

56. LACTATIONAL INDUCTION OF HYDROXYLATION OF CARCINOGENS IN SUCKLING RATS BY INDUCERS OF CYTOCHROME P1-450 (MEETING ABSTRACT).

Malejka-Giganti D, Ritter CL, Decker R
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Fed Proc; 41(6):1925 1982

Modification of carcinogen metabolism in suckling young (SY) through lactational transmittal of pharmacologically active compounds is of considerable interest. We have examined the effects of ip injections to lactating rats (LR) of 3-methylcholanthrene (3-MC) or beta-naphthoflavone (beta-NF) (40 mg/kg of b wt in corn oil for 3 days) on enzyme activities of hepatic microsomes (HM) of their SY. The levels of cytochromes P-450 (P1-450) and b5 and activities of NADH- and NADPH-cytochrome c reductases were similar to those of HM of SY from corn oil-treated LR. The apparent induction of cytochrome P1-450 in HM of SY of 3-MC- or beta-NF-treated LR was shown by the increased hydroxylations of benzo[a]pyrene (B[a]P) and N-2-fluorenylacetamide (2-FAA). In the presence of 0.1 mM alpha-NF (alpha-naphthoflavone), the levels of hydroxylation of B[a]P or 2-FAA were similar to

all 3 sets of SY and were 2.7-or 5.0-fold greater, respectively, than their basal levels. This suggests that although alpha-NF in vitro stimulates the basal hydroxylating enzyme activities, it inhibits the cytochrome P1-450-induced activities as it does in HM of LR. In the latter, alpha-NF was a more potent inhibitor than beta-NF. Binding to HM showed that beta-NF (type I) binds with a higher affinity than the type I substrates B[a]P and 2-FAA, whereas alpha-NF gives a qualitatively different binding spectrum suggestive of multiple binding sites. (no Refs)

57. EFFECT OF MONOOXYGENASE INDUCERS ON RAT MAMMARY PEROXIDASE AND ARYL HYDROCARBON HYDROXYLASE (AHH) (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:314 1982

Since horseradish peroxidase catalyzes binding of polycyclic aromatic hydrocarbons (PAH) by one-electron oxidation and peroxidase may activate PAH by the same mechanism, we studied the effect of monooxygenase inducers on rat mammary peroxidase, and compared it to induction of AHH. Female, 50-60 day-old Sprague-Dawley rats were treated for 2 days prior to killing with 5,6-benzoflavone (BF) or 3-methylcholanthrene (MC) by injection ip or sc at the second and fifth nipples on each side of the rat. BF and MC were injected ip in olive oil at 80 mg/kg and 40 mg/kg bw, respectively, and both sc at 50 nmole/nipple in 5 ul dimethyl sulfoxide (DMSO). Peroxidase and AHH were assayed with guaiacol and benzo[a]pyrene respectively, as substrates. Peroxidase was significantly induced by ip injection of BF and possibly of MC, when compared to untreated controls. Olive oil caused a smaller, but significant, increase in peroxidase activity. The effect of BF and MC injected sc was less certain, because of the increased peroxidase activity caused by DMSO. Olive oil ip and DMSO sc significantly reduced AHH. However, BF injected ip overcame the solvent effect and significantly increased AHH, compared to the untreated and solvent groups. MC injected ip, and BF and MC injected sc reversed some of the decrease in AHH caused by olive oil and DMSO. The effects of monooxygenase inducers on peroxidase were greater than those on AHH. (no Refs)

58. GENETIC DIFFERENCES IN THE INDUCTION OF ARYL HYDROCARBON HYDROXYLASE AND ITS COMPONENTS BY 3-METHYLCHOLANTHRENE IN LIVER AND LUNG MICROSOMES AMONG FOUR STRAINS OF GUINEA PIGS.

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Biochem Pharmacol; 31(12):2077 2082 1982

Four strains of guinea pigs (Hartley No 2, No 13 and JY-1) were examined for the effects of ip treatment with 3-methylcholanthrene on aryl hydrocarbon hydroxylase activity, total cytochrome P-450 content in liver and lung microsomes, and NADPH-cytochrome c reductase activity in liver microsomes. Following treatment with 3-methylcholanthrene at a dose of 50 mg/kg body wt, aryl hydrocarbon hydroxylase activity and cytochrome P-450 content in liver were both increased in all the strains used, and the activity of NADPH-cytochrome c reductase in liver was also increased in all strains except No 13. While the cytochrome P-450 content in lung was increased in all the strains except No 13, there was no increase in the aryl hydrocarbon hydroxylase activity in lung from any strain of guinea pig examined. When the dose of 3-methylcholanthrene was increased to 250 mg/kg body wt, an apparent induction of aryl hydrocarbon hydroxylase was detected in the lung from the Hartley strain of guinea pigs, but not in the other three strains. In summary, marked differences were seen in sensitivity to 3-methylcholanthrene between liver and lung, and apparent strain differences were observed among the guinea pigs used in this experiment. (Author abstract) (39 Refs)

59. COMPETITIVE HYDROCARBON INDUCTION OF AHH IN C3H 10T1/2 CELLS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:325 1982

We are studying the relative abilities of benz(a)anthracene (BA), 3-methylcholanthrene (3MC) and TCDD (2,3,7,8-tetrachlorodibenzoparadioxin) to induce cyt-P450 dependent benzo(a)pyrene metabolism (AHH (arylhydrocarbon hydroxylase)) in cultures of transformable C3H/10T1/2 mouse embryo fibroblasts. BA was found to be the most effective inducer of the three compounds; 13 uM BA (24 hr exposure) elicited a 7-10 fold increase in AHH activity. 10-7M TCDD gave a 2-fold induction, and no AHH increase was seen after exposure of the cells to 13 uM 3MC. All three compounds markedly induced C3H mouse liver AHH activity. As we and others have reported, the extent of induction seen in the 10T1/2 cell cultures was dependent upon the degree of cell confluence. Increasing concentrations of 3MC were able to totally suppress the induction seen with 13 uM BA alone in a dose related manner. Significantly higher concentrations of 3MC were required to suppress the induction when 26 uM BA was added to the medium. Based on these data, 3MC may be acting as a competitive antagonist (without eliciting a 3MC agonist reponse) at a receptor which mediates BA induction in these cells, or 3MC metabolites may be sufficiently toxic in these cells to prevent a normal induction response. (no Refs)

60. LIVER NEOPLASIA AND INDUCTION OF HEPATIC MIXED FUNCTION OXIDASE ENZYMES IN THE RAINBOW TROUT FOLLOWING DIETARY EXPOSURE TO BENZO(A)PYRENE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:226 1982

The influence of benzo(a)pyrene (BP) on the induction of certain enzymes within the hepatic mixed function oxidase (MFO) system and its potential carcinogenicity were examined in rainbow trout during a continuous dietary exposure. Nine week feeding trials were performed using 500 and 1000 ppm of BP to determine the maximum tolerated dose (MTD) without producing fish mortalities or growth inhibition. Levels of MFO enzymes including ethoxyresorufin-O-deethylase (EROD), ethoxycoumarin-O-deethylase (ECOD), arylhydrocarbon hydroxylase (AHH) and cytochrome P-450 were measured during this time. A feeding trial using a MTD of 1000 ppm was initiated in duplicate groups of 100 fingerling rainbow trout. Trout were sampled at 6, 12 and 18 months for necropsy and subsequent gross and histological examination of internal organs. Mean MFO enzyme levels of EROD, ECOD, and AHH were significantly elevated showing dose and time response relationships when compared to those of fish fed a BP-free diet. P-450 levels in BP-fed fish increased only slightly. At 12 months 15% of the BP-fed fish had histologically confirmed neoplastic lesions of the liver. After 18 months 20% gross lesions were observed,

histological confirmation is in progress. No evidence of neoplasia was observed in control fish. These results indicate that in rainbow trout BP is a potent inducer of certain hepatic MFO enzymes and is a hepatocarcinogen when fed continuously in the diet. (no Refs)

61. STUDIES ON THE MECHANISM BY WHICH BENZO(A)PYRENE INHIBITS EPIDERMAL GROWTH FACTOR BINDING TO CELLULAR RECEPTORS (MEETING ABSTRACT).

Ivanovic V, Okin E, Weinstein IB
Health Sciences Center, Columbia University, New York, NY, 10032
Proc Am Assoc Cancer Res; 23:221 1982

We have previously shown that benzo(a)pyrene (BP) and other inducers of cytochrome P-450 inhibit binding of epidermal growth factor (EGF) to cell surface receptors in C3H 10T1/2 mouse fibroblasts. In the present study a Scatchard analysis revealed that BP treatment acts mainly by reducing the effective number of both high and low affinity receptors. To further understand the mechanism of action we analyzed the role of BP metabolites in BP-mediated inhibition of EGF binding. Confluent 10T1/2 cells were exposed to 1uM 3H-BP for 24 hrs and the ethyl acetate extract of the medium was analyzed by high-pressure liquid chromatography (HPLC). The HPLC profile indicated that about 90% of the recovered radioactivity was unmetabolized BP. The remaining radioactivity represented the following metabolites: BP-9,10-diol, BP-7,8-diol, BP-3,6-quinone, BP-9-phenol, and BP-3-phenol. Equimolar concentrations (1-4uM) of these metabolites, and of several other BP phenols and BP quinones exhibited less inhibition of EGF-receptor binding than that obtained with BP. In view of the latter results, the relatively small amounts of BP metabolites compared to the parent compound in 10T1/2 cultures, and the inability of the ultimate metabolite BP-7,8-diol-9,10 oxide to inhibit EGF binding, it seems likely that BP itself rather than a metabolite(s) is responsible for the inhibition of EGF binding. The effects of BP on this membrane-associated receptor may be related to its ability to act as a complete carcinogen. (no Refs)

62. DIFFERENTIAL RATE OF IN VIVO DNA REPAIR SYNTHESIS IN LUNG AND LIVER OF MICE FOLLOWING BENZO(A)PYRENE (BP) TREATMENT (MEETING ABSTRACT).

Kulkarni MS, Angerman-Stewart J, Anderson MW
National Institute of Environmental Health Sciences/National Institute of Health, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:255 1982

A/HeJ mice are susceptible to BP-induced pulmonary neoplasia whereas the liver is resistant to it. We have previously demonstrated that the formation and disappearance of BP-DNA adducts in A/HeJ mice in vivo are similar in lung and liver. In the present investigations, BP-induced unscheduled DNA synthesis (UDS) was examined in vivo in lung and liver of A/HeJ mice. Following BP treatment, 3H-thymidine incorporation was measured using hydroxyapatite column chromatography and trichloroacetic acid (TCA) precipitation of phenol-extracted DNA, and also by autoradiography. Mice were given BP (po 0.3 mg per mouse) by gavage, and two hours prior to sacrifice 3H-thymidine was administered by ip. DNA replication was differentiated by total DNA repair synthesis by the use of hydroxyurea (HU). Animals were sacrificed at different time points from 4-72 hours following BP dose. Replication and UDS were measured by DPM/mg total DNA. We found in reproducible experiments that BP caused minimum or no UDS in lung whereas in liver UDS was significant at all time points examined (ie, approx 3,000 dpm/mg DNA at 24 hours). DNA synthesis and UDS were further differentiated by in vivo autoradiography. Autoradiographs of one micron thick lung and liver tissues support the above data. These different rates of DNA repair synthesis could be one of the factors for tissue-susceptibility to BP induced neoplasia. (no Refs)

63. THE IN VITRO EFFECT OF BENZO-PYRENE ON THE IMMUNE RESPONSE (MEETING ABSTRACT).

Rossi RM, Urso P, Gengozian N
Medical and Health Sciences Division, ORAU, Oak Ridge, TN, 37830
Fed Proc; 41(3):446 1982

The potent carcinogen, benzo(a)pyrene (BP), was shown to decrease the in vitro ability of mouse (C3H) spleen cells to respond to a foreign antigen, (sheep red blood cells (SRBC)). At concentrations as low as 10(-8) molar, BP inhibited the antigen-antibody response as measured by a reduction in the plaque forming cells (PFC) determined by using a modified Jerne plaque technique. The maximal inhibition was obtained at 4 x 10(-4) molar, (100%), with a gradual reduction occurring in the range of 10(-8) to 10(-5) molar. Lower concentrations resulted in no inhibition or a slight enhancement of the PFC response. The noncarcinogenic analog of benzo(a)pyrene, benzo(e)pyrene (B(e)P), produced no inhibition between 10(-5) and 10(-7) molar. Further, 10(-4) and 10(-6) M BP severely depressed the mixed lymphocyte response of normal spleen cells. A single dose of BP, (150 ug/g body weight), during gestation, resulted in a severe depression of the anti-SRBC PFC response that persisted throughout life. These results indicate that exposure of immunocompetent (T and B) cells to small doses of BP disrupt events leading to humoral and cell mediated immune responses. (no Refs

MODIFICATION OF THE EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS

64. DIFFERENTIAL EFFECTS OF RETINOIC ACID AND 7,8-BENZOFLAVONE ON THE INDUCTION OF MOUSE SKIN TUMORS BY THE COMPLETE CARCINOGENESIS PROCESS AND BY THE INITIATION-PROMOTION REGIMEN.

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Cancer Res; 42(9):3521-3525 1982

The present study was designed to elucidate differences in the mechanism of the induction of mouse skin tumors either by the initiation-promotion regimen or by the complete carcinogenesis process. The protocols used to elicit skin tumors were: (a) by the initiation-promotion regimen, a single application of 0.2 umol of 7,12-dimethylbenz[a]anthracene (DMBA) followed by twice-weekly applications of 12-O-tetradecanoylphorbol-13-acetate (TPA); and (b) by the complete carcinogenesis process, a single application of 3.2 umol of DMBA without TPA treatment, or 0.2 umol of DMBA applied once weekly, or 1, 10, 50, or 100 nmol of DMBA applied twice weekly without application of TPA. The biology of tumor formation by the initiation of tumors with a single application of 0.2 umol DMBA fol-

lowed by twice-weekly applications of TPA differs from tumor induction by once-weekly 0.1-umol doses of DMBA. In the latter case, papillomas developed more slowly and were less common (the tumor induction time was long; tumor yield was less), but carcinomas appeared much earlier. Retinoic acid, a potent inhibitor of tumor promotion by TPA, failed to inhibit and under some experimental conditions significantly (p less than 0.001) enhanced tumor formation by DMBA. Also retinoic acid did not inhibit ornithine decarboxylase induction by DMBA. In contrast, 7,8-benzoflavone, which did not inhibit the induction of ornithine decarboxylase activity by TPA, inhibited the induction of ornithine decarboxylase activity and tumor formation by DMBA. The results indicate that the nature and the mechanism of the biochemical events elicited by the presumed promoting component of carcinogenesis by a complete carcinogen are different from those of the tumor promoter TPA. (Author abstract) (21 Refs)

65. 7,12-DIMETHYLBENZ-(ALPHA)ANTHRACENE (DMBA) CARCINOGENICITY: MODERATION BY SUPPLEMENTAL BETA CAROTENE (B-CAR) AND VITAMIN A (VIT A) (MEETING ABSTRACT).

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Fed Proc; 41(3):67 1982

Because B-Car inhibits tumor development due to Moloney Sarcoma Virus and C3HBA adenocarcinoma, there is interest in the possible prevention of other tumors by B-Car. Previously we showed that B-Car, given 2 days before DMBA, inhibited DMBA carcinogenesis. We report now the effect of B-Car and Vit A supplementation, started either 1 or 2 weeks after DMBA. One hundred female SD (Sprague-Dawley) rats (180 g) maintained on Purina Lab chow (Vit A + B-Car content - 18,000 units Vit A/Kg diet) received 20 mg DMBA in 1 ml corn oil by stomach tube. Treatments were begun one week later: a) no treatment, b) Vit A supplementation (150,000 units/Kg diet), c) B-Car supplementation (90 mg/Kg diet). One additional group, d), was started on supplemental Vit A the second week after DMBA and one, e), on supplemental B-Car at this time. The results after 22 weeks based on groups of 20 rats each: deaths -4 in group a; rats with tumors -19 in group a, 3 in b, 4 in c, 3 in d, and 4 in e; and tumors/group -30 in group a, 3 in b, 5 in c, 4 in d, and 6 in e. We conclude: B-Car and Vit A are active in preventing DMBA tumors, even when supplementation is started two weeks after DMBA administration. (no Refs)

66. INHIBITORY ACTION OF BHA ON CARCINOGENESIS IN F1 AND F2 DESCENDANTS OF MICE EXPOSED TO DMBA DURING PREGNANCY.

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Int J Cancer; 29(1):121-124 1982

Administration of 500 ug of 7,12-dimethyl benz(a)anthracene (DMBA) to female mice during late pregnancy results in the occurrence of tumors in F1 and F2 generation individuals. F1 progeny had a higher percentage of tumor-bearing individuals than the F2 progeny. All the five litters of F1 females displayed tumor risk but the risk declined progressively in successive litters. Perinatal administration of BHA to the pregnant mice (P generation) receiving 500 ug of DMBA would result in significant reduction in tumor risk among the individuals of F1 generation ($p < 0.01$) and F2 generation ($p < 0.05$). (Author abstract) (43 Refs)

67. EFFECTS OF ARGININE ON THE CARCINOGENICITY OF N-METHYL-N-NITROSOUREA (MNU) AND 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:271 1982

Female Sprague-Dawley rats were used to investigate the effects of dietary arginine on the occurrence of mammary tumors induced by DMBA and MNU. Sixty rats were fed either a control 14% casein diet or the same diet supplemented with 5% arginine starting at 36 days of age. At 50 days of age, 30 rats from each treatment were intubated intragastrically with 7.5 mg DMBA in sesame oil. The remaining 30 in each treatment were given MNU (40 mg/kg body weight) via the jugular vein. Mammary tumors were detected by weekly palpation from 5-18 weeks after carcinogen administration. Dietary arginine supplementation did not alter food intake or weight gain. Total palpable mammary tumors for each group increased at a linear rate. For DMBA-treated rats the rate was 8.1 new palpable tumors per week for controls compared to 4.7 for arginine-supplemented rats. The respective rates were 8.9 and 6.8 tumors/week for MNU-treated rats. In DMBA-treated rats the time for 50% of the rats to develop tumors was increased from 9.3 to 12.5 weeks by dietary arginine supplementation, whereas in MNU-treated rats this time was not affected by arginine. Eighteen weeks after DMBA, 23 control and 21 arginine supplemented rats had tumors and after MNU the corresponding numbers were 27 and 23. The greater inhibition by arginine of DMBA- than MNU-induced tumor formation indicates that arginine may inhibit the activation of procarcinogens (DMBA). (no Refs)

68. INHIBITORY EFFECT OF A FAT-FREE DIET ON MAMMARY CARCINOGENESIS IN RATS.

Davidson MB, Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 3(4):207-215 1982

Young female Sprague-Dawley rats were administered 7,12-dimethylbenz(a)anthracene, and a wk later the rats were transferred from commerical feed to a semipurified diet containing 20% corn oil. Eight wk after receiving the carcinogen, half of the rats were changed to a fat-free diet to determine the effects on mammary tumor growth and development. After another 20 wk, rats fed the fat-free diet had significantly fewer tumors per tumor-bearing rat and the tumors were smaller than those of rats that continued on the high-fat diet. Rats fed the fat-free diet weighed somewhat less but showed no physical evidence of essential fatty acid deficency. Tumors regressed in about half of the rats on the fat-free diet and in some cases became nonpalpable. After 28 wk on this diet, the remaining rats were transferred back to the high-fat diet and subsequently showed a marked stimulation in tumor growth and development. This continued even after the rats were returned to the fat-free diet 8 wk later, indicating that the tumors were no longer susceptible to the deprivation of dietary fat. The results of this study provide further evidence that dietary fat affects the promotional stage of mammary carcinogenesis. (Author abstract) (25 Refs)

69. INFLUENCE OF BCG ON LUNG CARCINOGENESIS (MEETING ABSTRACT).

DeCaro L, Lemon W, Paladugu RR, Benfield JR
City of Hope National Medical Center, Duarte, CA, 91010
Proc Am Assoc Cancer Res; 23:989 1982

Although BCG has been used for adjuvant therapy of lung cancer in humans, scientific basis is incomplete. We have tested the effect of adjuvant BCG during carcinogenesis in a hamster model with the hypothesis that non-specific immunopotentiation will modify the rate of carcinogenesis. Syrian golden hamsters, 8-10 weeks old, received benzopyrene (BP) by localized endobronchial implants from where BP was released in sustained fashion. This approach is known to produce focal cancers. All animals were sensitized with 0.5 Keyhole Limpet Hemocyanine (KLH) to permit recall response measurements. Test group (30) received BCG; control group (30) no-BCG. Animals from each group (10) were sacrificed at 60 day intervals 48 hours after KLH challenge for recall response. Results showed that during bronchial carcinogenesis in hamsters, adjuvant BCG did not significantly alter the rate of carcinogenesis. (no Refs)

70. A 'WINDOW EFFECT' IN THE ABILITY OF ANTHRALIN TO REVERSE INITIATION IN TWO-STAGE MOUSE SKIN TUMORIGENESIS (MEETING ABSTRACT).

De Young LM, Nelmes CT, Knowlton FM
Syntex Research, Palo Alto, CA, 94304
Proc Am Assoc Cancer Res; 23:347 1982

Low doses of anthralin applied between initiation and the beginning of promotion reduce the number of papillomas (Pa)/mouse as compared to non-anthralin-treated controls. We now describe a specific period or 'window' during which a single treatment with 20 ug anthralin can partially reverse initiation. Mice were initiated with 51.2 ug 7,12-dimethylbenz(a)anthracene and beginning 4 weeks later were promoted with 5.25 ug 12-O-tetradecanoyl-phorbol-13-acetate 2x weekly for 18 weeks. The control group had 13.2 Pa/mouse at the end of promotion. In additional experiments neither repeated 20 ug doses nor higher doses of anthralin gave greater tumor inhibition than a single 20 ug application 7 days post-initiation. When 10 ug mezerein were applied 7 and 14 day post-initiation there was a 15% reduction in Pa/mouse. We are currently investigating this effect at higher doses of mezerein. Anthralin does not inhibit the early events of initiation. There is a window for the first 10 days after initiation during which initiation is reversible by anthralin and possibly by mezerein. (1 Ref)

71. SUBMANDIBULAR GLAND REMOVAL INCREASES TUMORIGENESIS IN MALE CD-1 MICE (MEETING ABSTRACT).

O'Connell JF, Weiss HS, Pitt JF, Miller RE, Graff DE
Department of Physiology, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1548 1982

Two wks after surgical removal of the submandibular-sublingual complex, tumors were induced on the shaved back via a two stage system. Initiation was with 0.05mg benzo(a)pyrene in acetone in one wk and promotion by repetitive weekly doses of either 2ug (trial 1) or 4ug (trial 2) of 12-O-tetradecanoyl-phorbol-13-acetate (TPA). In the first trial mice without the gland complex reached 50% incidence approximately 3 weeks earlier (18 vs 21) and had a 3 times higher rate of increase in the number of tumors per mouse wk than sham operated mice. In the second trial (4ug TPA) mice without the gland complex reached 50% incidence when sham operated and intact controls had 32% and 29% incidence, respectively. There was no significant change in tissue to appearance of first tumor among treatment groups. Increased tumorigenesis in mice without the gland complex appears unrelated to differences in food consumption or body weight, but might be related to the gland's production of several peptides, including epidermal growth factor. (no Refs)

72. EFFECT OF CASTRATION ON EXPERIMENTAL TUMOR INDUCTION BY 7,12-DIMETHYLBENZANTHRACENE (DMBA) IN WISTAR RATS AND SYRIAN GOLDEN HAMSTERS.

Perez Mingvez F, Lleonart Bosch A
Departamento de Patologia, Universidad de Valencia, Valencia, Spain
Oncologia; 5(2):89-92 1982

The effect of castration on the incidence and distribution of DMbA-induced tumors was studied in female Wistar rats and female Syrian golden hamsters. DMBA was administered intragastrically, the total dose, administered in 6 days, being 20 mg for rats and 16 mg for hamsters. Tumor incidence was 27/28 for castrated hamsters, 23/30 for noncastrated hamsters, 25/30 for castrated rats and 28/29 for noncastrated rats. The most frequent tumors found in noncastrated rats were breast tumors, accounting for 68% of all tumors in these animals, while the incidences were lower for tumors of the skin (6%), hemolymphatic tissue (3%) and kidneys (7%). Breast tumors accounted for only 9% in the castrated rats, while tumors of the hemolymphatic tissue accounted for 40%. The incidences of the other tumors showed no significant differences between castrated and noncastrated rats. The most frequent tumors in noncastrated hamsters were those of the ovaries (26%), followed by kidney tumors (16%), skin tumors (9%) and breast tumors (8%). Skin tumors (46%) were most frequent in the castrated hamsters, while the other tumors were rare: tumors of the breast and hemolymphatic tissues accounted for 9% and 8%, respectively. The findings indicate the influence of castration on the incidence of skin tumors leukemias and lymphomas, as well as of skin tumors in hamsters. (67 Refs) (In SPA)

73. TWO-STAGE CARCINOGENESIS ON SKIN AND IN INTERNAL ORGANS OF C57BL/B6 MICE (MEETING ABSTRACT).

Yamasaki H, Cabral JR, Galendo D, Tomatis L
International Agency for Research on Cancer, Lyon, France
Toxicologist; 2(1):63 1982

Promoting effect of phorbol esters, as represented by 12-O-tetradecanoyl phorbol-13-acetate (TPA), has been extensively studied on mouse skin, using a conventional initiation-promotion protocol. Since it has been shown that these tumor promoters exert a variety of biological and biochemical effects on the cells derived from various tissues other than mouse skin, it was of our interest to examine the promoting activity of TPA on internal organs as well as on skin. When fifty C57BL/B6 mice, 6 week old, were painted once with 3 mg of benzo(a)pyrene (B(a)P and painted with 5 ug of TPA twice a week, 64% of mice developed papillomas by 30 weeks of treatments, whereas none of control groups, treated with B(a)P alone or TPA alone, developed papillomas. These results confirm that C57BL/B6 mice are reasonably sensitive to a conventional two-stage carcinogenesis protocol. However, when the same amount of B(a)P was injected subcutaneously to pregnant mothers and their descendants were painted on skin of the

back with 5 ug of TPA twice a week from weaning for 93 weeks, no persistent papilloma was observed. Similarly, the transplacentally exposed mice were injected intraperitoneally with 5 to 10 ug of TPA twice a week. After 100 weeks, the number of mice that died with tumor (4/63) was not significantly different from that in the group without TPA injection (3/64). Taken together, these results suggest that under the experimental conditions used, a conventional mouse skin initiation-promotion carcinogenesis is demonstrable, but transplacental initiation-postnatal promotion of skin and internal organs has not been clearly observed so far in C57BL/B6. (no Refs)

74. 3H-BENZO(A)PYRENE (3H-BAP) METABOLISM BY LUNG AND LIVER MICROSOMES FROM NAPHTHALENE-TREATED MICE (MEETING ABSTRACT)

Rasmussen RE, Witte ME
Department of Community and Environmental Medicine, University of California, Irvine, CA, 92717
Proc Am Assoc Cancer Res; 23:319 1982

Naphthalene (N) is a common industrial chemical and a component of tobacco smoke that causes necrosis of the nonciliated bronchiolar epithelial (Clara) cells of the mouse when given at high doses (greater than 200 mg/kg (body wt) bw). The time course of this effect has been studied in BC3F1/Cum mice in terms of histological changes in the bronchiolar epithelium and the metabolism of 3H-BaP to hydroxylated derivatives by microsomes from lung and liver. Mice were treated ip with N dissolved in corn oil (250 mg/kg bw) and killed at intervals up to 9 days post-treatment. Microsomes were incubated for 30 min with 3H-BaP and metabolites were analyzed by thin layer chromatography and scintillation counting. Following N treatment, 3H-BaP metabolism by lung microsomes declined by more than 90%, reaching a minimum at 72 hours post-treatment. By 9 days, some recovery had occurred, but not to control levels. Treatment of mice with beta-naphthoflavone (BNF, 80 mg/kg bw) increased the microsomal enzyme activity in lungs of both control and N-treated mice to about the same extent. Histological studies showed that the reduced metabolism of 3H-BaP by lung microsomes was correlated with the loss of the Clara cells. There was no effect of the N treatment on liver microsome activity or histology, nor was there any difference between male and female mice. (no Refs)

75. EFFECTS OF ESTRADIOL ON ENZYMES ASSOCIATED WITH BENZO(A)PYRENE METABOLISM (MEETING ABSTRACT).

Williams MT
Department of Biochemistry, University of South Florida, College of Medicine, Tampa, FL, 33612
Fed Proc; 41(3):1428 1982

Injection of female C57Bl/65 mice with estradiol (E2) 24 hours prior to, during and 72 hours after injection of 3-methylcholanthrene (3-MC) resulted in an apparent decrease in hepatic aryl hydrocarbon hydroxylase (AHH) activity when compared to AHH activity from animals receiving injection of 3-MC only. Moreover, AHH mediated binding of benzo(a)pyrene (BP) metabolites to DNA was inhibited between 35 and 45% in the 3-MC-E2 treated animals as compared to the 3-MC treated animals. The post-105,000 xg supernatant from E2 treated animals exhibited significantly higher glutatione S transferase activity compared to supernatants from control animals. AHH activity in microsomes from control, E2 and 3-MC treated animals was significantly inhibited by BP quinones at a concentration as low as 2uM. AHH activity in microsomes from E2 treated animals was more sensitive to inhibiton by quinones than control AHH activity. Our data suggest that E2 may exert a direct inhibitory effect on hepatic AHH activity and also affect the activities of other enzymes associated with detoxification and inactivation of xenobiotics. (no Refs)

76. PROTECTIVE EFFECTS OF THE HERBICIDE TRIFLURALIN ON BENZO(A)PYRENE INDUCED PULMONARY ADENOCARCINOMA AND FORESTOMACH PAPILLOMAS IN FEMALE A J MICE (MEETING ABSTRACT).

Triolo EA, Lang WR, Kratky MT, Triolo AJ
Departments of Pharmacology and Pathology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, 19107
Fed Proc; 41(3):1548 1982

Mice were fed trifluralin (TF) at 1000, 1500, and 2000 ppm in the diet for 12 or 14 weeks. Tumors were induced by administering 3 mg of benzo(a)pyrene (BP) orally at two time periods. An inhibition of tumorigenesis in lung and forestomach by TF was observed when this herbicide was fed in the diet starting either one week before or one week following exposure to BP. Lung tumors were identified as bronchioloalveolar adenocarcinoma and forestomach tumors as squamous cell papillomas. BP is generally considered to be carcinogenic by virtue of its transformation by microsomal enzymes into chemically reactive intermediates which bind to critical macromolecules of target organs susceptible to tumors. Arylhydrocarbon hydroxylase (BP hydroxylase), a microsomal mixed-function oxygenase, was significantly increased in target (lung and forestomach) and in non-target (glandular stomach) organs when mice were fed TF for a duration of 14 weeks. No significant effects of TF were observed on hepatic enzyme activity. TF was found to decrease the binding of H3-BP to certain liver macromolecules. These findings suggest that various mechanisms resulting from TF treatment may be involved in the observed protection against BP-induced tumors. (no Refs)

INDUCTION OF NEOPLASMS IN EXPERIMENTAL ANIMALS

77. INDUCTION OF CARCINOMA OF GALLBLADDER IN HAMSTERS BY INSERTION OF METHYLCHOLANTHRENE BEESWAX PELLETS.

Suzuki A, Watanabe M, Takahashi T
Dept. Surgery, Koto General Hosp., Akita, 018-16, Japan
Jpn J Surg; 12(3):227-228 1982

Successful induction of gallbladder cancer in female hamsters is reported. The animals were subjected to insertion of a pellet into the gallbladder. The pellet contained either beeswax alone (B group) or beeswax mixed with methylcholanthrene (MC-B group). The animals were sacrificed 171-201 days (B group) or 145-226 days (MC-B group) after insertion. Gallbladder carcinomas were observed in 9/23 hamsters in MC-B group and in 0/32 hamsters in B group. Dysplasia of the gallbladder epithelium was detected in three hamsters in MC-B group and in four hamsters in B group. (3 Refs)

78. TUMOR INITIATION IN FETAL SKIN CELLS OF HA/ICR SWISS MICE EXPOSED TRANSPLACENTALLY TO 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Morris EP
New York University, New York, NY
Diss Abstr Int [B]; 42(7):2660-B 1982

Fetal skin cells can be initiated by exposing mice to DMBA (7,12-dimethylbenzanthracene) during gestation. This experiment was designed to determine if the number of skin cells initiated in a mouse was proportional to the number of cells in the organ at the time of exposure. Fetal and adult exposures were compared to ascertain if the time elapsed from fetal initiation to adulthood affected the tumor yield or type of tumors that developed in the adult. These goals were accomplished using a modified initiation-promotion, or two-stage mouse skin tumorigenesis protocol. The carcinogen converts normal cells into initiated cells. The application of the promoting agent, TPA, (12 O-tetradecanoyl-phorbol-13-acetate) permits the detection of initiated cells by stimulating them to proliferate and form glossy visible papillomas. The carcinogen was administered by gavage to the mother during gestation or to adult mice; the promoter was applied to the skin of the mice beginning at nine weeks of age. Tumor yields, expressed as average number of papillomas per mouse were charted as a function of time from the start of promotion. The histopathological characterization of tumors after pre- or postnatal initiation was the same. For a given treatment regime, males and females showed approximately the same tumor yield. Lymphoma and lung tumor occurrence was associated with carcinogen exposure rather than TPA or acetone exposure. Proportionality between cells at risk and tumor yields was observed following exposure of day 12 or older fetuses and adults. The tumor yield of mice exposed on day 9 was higher than expectations based on proportionality; this may indicate a heightened sensitivity or may be dose related. The data suggest that the number of epidermal basal cells at risk for DMBA tumorigenesis after day 9 of fetal development is approximately proportional to the number of cells present in the organ at the time of exposure. (no Refs)

79. AN EXPLANATION FOR THE PROPORTION OF CARCINOMAS AND SARCOMAS SEEN IN CHEMICALLY INDUCED MURINE SUBMAXILLARY GLAND TUMORS.

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Cancer 50(3):531-542 1982

Pellets of 1 mg 9,10-dimethyl-1,2-benzanthracene (DMBA) were implanted into the submaxillary glands of 53 male C57BL/6J mice, and groups of mice were autopsied weekly or biweekly thereafter. Histologic evidence of tumor was noticed first at 12 wk. From 16 wk onwards, the submaxillary glands of all mice autopsied contained either carcinoma (3 animals) or sarcoma (10 animals); 8/8 attempts to transplant these tumors in C57BL/6J mice were successful. Of the resulting eight tumor lines, two carcinomas and two fibrosarcomas were transplanted for over 30 mo. Within the first few transplant generations, all four tumors showed an increase in growth rate and in histologic evidence of anaplasticity. For the particular tumors selected for study, the two carcinomas differed from the two sarcomas by growing more slowly, requiring more cells for tumor takes, and possessing a higher immunogenicity. These results may explain the types of tumors generated in submaxillary gland carcinogenesis. Carcinomas appear first, since they develop from the epithelial cells into which the carcinogen is implanted. Later, when fibroblasts wall off the carcinogen, fibroblasts are at risk for neoplastic conversion. Because of the more aggressive nature of the resultant fibrosarcoma cells, sarcomas may overgrow some early carcinomas. (Author abstract) (33 Refs)

80. BREAST TUMORS INDUCED BY N-NITROSOMETHYLUREA (NMU) OR DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN CASTRATED MALES: ROLE OF HIGH FAT DIET (MEETING ABSTRACT).

Rivenson A, Silverman J, Weisburger J
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:275 1982

We attempted to extend the findings of Fingerhut and Veenema on the induction of prostate cancer in gonadectomized male Fischer F-344 rats on 20% and 5% fat diets, utilizing iv dosing with 7,12-dimethylbenz(a)anthracene (DMBA), and also 2',3-dimethyl-4-aminobiphenyl (DMAB), and N-nitrosomethylurea (NMU). No prostate cancers were found in rats held for 68 weeks. However, with NMU and DMAB these gonadectomized male rats had breast cancers in a higher incidence on the 20% fat diet with NMU but not with DMAB. All neoplasms were malignant, with invasion and destruction of neighboring tissues, and presenting histologically mixed glandular and squamous structures, quite distinct from lesions usually seen in females. Similar type of adeno-squamous carcinomas could be seen in tumors of the ear duct (Zymbal glands) and bulbo urethral glands developed in rats given the above carcinogens. The topographic location of the tumors labeled grossly as 'breast tumors' excluded other possible similar glandular structures and also a sweat glard tumor since the rat skin does not contain sweat glands. Other tumors noted after the carcinogens given iv were: bladder, DMAB only; small intestine and colon, NMU and DMAB, lung, DMBA, NMU, and DMAB; sarcoma, NMU and DMAB; stomach NMU. Several of these cancers exhibited metastases. None of the tumors noted above were present in controls. In summary, NMU and DMAB induced tumors in a number of sites, but selectively caused mammary gland adenocarcinoma and adenosquamous carcinoma, and Zymbal gland adenoepidermoid carcinoma. (1 Ref)

81. INTERCARCINOGEN COMPARISON IN HAMSTER LUNG CANCER (MEETING ABSTRACT).

Hammond W, Shors E, Paladugu R, Cohen A, Fu P, Benfield J
City of Hope Medical Center, Duarte, CA, 91010
Proc Am Assoc Cancer Res; 23:217 1982

The polycyclic aromatic hydrocarbons Benzo(a)pyrene (BP), 7,12-Dimethylbenzanthracene (DMBA), and 20-Methylcholanthrene (MCA) have generally been considered comparable. We have used them as focal bronchial carcinogens via sustained release implants (SRI) of silicone polymer in the right lower bronchus of Syrian Golden hamsters. SRI were 1.5 mm diameter and weighed 9.0+/-1.0 mgm; they contained either 5 or 10% w/w carcinogen. At intervals up to 33 wks, groups of hamsters were sacrificed and the bronchial histology studied. An orderly progression of histologic change through basal and columnar hyperplasia, squamous metaplasia, and atypia to carcinoma-in-situ and invasive squamous cell carcinoma was induced by 10% BP and 10% MCA. Cancers were first noted 14 wks after implantation with 10% BP and after 16 wks with 10% MCA. Nine of 12 animals examined from 16-28 wks had cancer from 10% MCA, and 11 of 11 developed cancer from 10% BP between 14-33 wks. In contrast, the dominant histologic pattern noted from 5% and 10% DMBA was that of inflammation and loss of bronchial epithelium, with only occa-

sional metaplasia or atypia. Cancer from 10% DMBA was first noted at 17 wks, but only 1 of 8 animals studied from 17-26 wks developed cancer. A neurofibrosarcoma developed from 5% DMBA at 26 wks. No cancers were found in 9 other animals sacrificed between 26-29 wks while 2 animals surviving more than 55 wks had squamous cell carcinoma. Attrition during carcinogenesis was 10% from 10% MCA (5/53) and was 9% from 10% BP (4/45), while that from 10% DMBA was 49% (31/63). Attrition from 5% DMBA was zero. (no Refs)

82. TUMORIGENICITY OF ENANTIOMERS OF THE DIASTEREOMERIC BAY-REGION CHRYSENE 1,2-DIOL-3,4-EPOXIDES ON MOUSE SKIN AND IN NEWBORN MICE (MEETING ABSTRACT).

Chang RL, Levin W, Wood AW, Yagi H, Tada M, Vyas KP, Jerina DM, Conney AH
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Proc Am Assoc Cancer Res; 23:216 1982

The tumorigenicity of chrysene, (+)- and (-)-chrysene 1,2-dihydrodiol and the (+)- and (-)-enantiomers of the diastereomeric bay-region chrysene 1,2-diol-3,4-epoxides were assessed in two tumor models. Initiation-promotion experiments on mouse skin revealed that (-)-chrysene 1,2-dihydrodiol had approx 2 times the tumor-initiating activity of chrysene while the (+)-enantiomer had no significant activity. Of the 4 isomers of the chrysene 1,2-diol-3,4-epoxides, only the (+)-isomer-2, in which the benzylic hydroxyl group and epoxide oxygen are trans, had significant tumorigenic activity. The (+)-diol epoxide-2 isomer had tumor-initiating activity that was equivalent to the parent hydrocarbon. In newborn mice, a total dose of 0.7 or 1.4 umol of hydrocarbon was administered, and tumorigenic activity was determined when the mice were 37-41 weeks old. Animals treated with (+)-diol epoxide-2, (-)-1,2-dihydrodiol or racemic 1,2-dihydrodiol had an average of 7.2, 6.5 and 2.5 lung tumors/mouse/umol of compound administered, respectively. The parent hydrocarbon and all other derivatives were essentially inactive in producing an increased incidence of lung tumors above the controls (0.13 lung tumors/mouse). With respect to hepatic tumors in male mice, (-)-1,2-dihydrodiol was the most active compound which produced 3-, 4-, 6-, and 10-fold more tumors than did (+)-diol epoxide-2, racemic 1,2-dihydrodiol, chrysene and (+)-1,2-dihydrodiol, respectively. The other 3 diol epoxides had no hepatotumorigenic activity (no Refs)

83. THE SYNTHESIS AND CARCINOGENIC ACTIVITY OF 9-METHYLBENZO(A)PYRENE, TRANS-7,8-DIHYDROXY-9-METHYL-7,8-DIHYDROBENZO(A)PYRENE AND TRANS-9,10-EPOXY-7,8-DIHYDROXY-9-METHYL-7,8,9,10-TETRAHYDROBENZO(A)PYRENE.

Lyga JW
The Ohio State University, Columbus, OH
Diss Abstr Int [B]; 42(10):4066-B 1982

The synthesis of the title compounds was achieved and their carcinogenic activity was investigated. The new synthesis of 9-methylbenzo(a)pyrene was developed starting from 1-formylpyrene. The dihydro-diol and diol-epoxide were synthesized from 9-methyl-7-oxo-7,8,9,10-tetrahydrobenzo(a)pyrene using existing methodology. Mice subjected to topical application of the above compounds had few or no tumors while the non-methylated compounds produced substantial tumors. It is believed that the methyl group prevents the reaction of biological nucleophiles with the 9,10-epoxide (no Refs)

84. RADIOBIOLOGICAL EQUIVALENT OF BENZO(A)PYRENE CARCINOGENICITY DURING INHALATION EXPOSURE.

Knizhnikov VA, Grozovskaia VA, Barkhudarov RM, Novikova Nia, Bugrova NV
No affiliation given
Gig Sanit; (7):23-27 1982

To evaluate the radiobiological equivalent of benzo(a)pyrene (BP) carcinogenicity, random-bred female albino mice were subjected to inhalation exposure to BP aerosol (6 hr/day, 5x/wk, for 3 mo). BP concentration in exposure chambers was 0.2 (Group 1), 6.3 (Group 2) and 78 ug/cubic meter (Group 3). The animals were followed-up until their natural death. Av concentration of BP in the lung tissue in the animals from Group 1, 2, and 3 was 0.02, 0.8, and 9.0 ug/g, respectively. The mice subjected to inhalation exposure to BP developed lung carcinomas, lymphosarcomas, and adenocarcinomas. The histology of BP-induced lung tumors was identical to that of human lung cancer. These findings indicate that the yield of BP-induced lung tumors can be approximated by the exponential curve, and that the carcinogenicity of BP after inhalation exposure was significantly greater than that after other methods of intratracheal administration. (16 Refs) (In RUS)

85. DERMAL CARCINOGENESIS BIOASSAYS OF DIESEL PARTICULATES AND THEIR DICHLOROMETHANE EXTRACT (MEETING ABSTRACT).

DePass LR, Chen KC, Peterson LG, Weil CS
Bushy Run Research Center, Export, PA
Toxicologist; 2(1):63 1982

Diesel particulates and dichloromethane extract of diesel particulates were tested to assess their potential as complete carcinogens and as initiators or promoters of carcinogenesis. The test agents were applied as suspensions to the dorsal skin of male C3H mice at the highest doses that were non-irritating and sufficiently flowable for application. Lower concentrations were also used to obtain information on the dose-response relationships. Acetone was used as the vehicle in all studies; diesel particles were applied in 10% or 5% concentrations, and dichloromethane extract was administered as 50%, 25%, 10%, or 5% suspension. Dosing was performed 3 times per week in the initiation and complete carcinogenesis studies, and 5 times per week in the promotion studies. Positive control groups received repeated application of 0.2% benzo(a)pyrene (B(a)P) for complete carcinogenesis or a single application of 1.5% B(a)P, or 10% particulates or 50% of particulate extract suspensions, followed by repeated application of 0.0001% phorbol myristate acetate (PMA) for the initiation studies. In promotion studies, repeated application of PMA was replaced by 10% suspension of diesel particulates or 50% and 25% of extract suspensions. The test agents were applied similarly in place of B(a)P in the complete carcinogenesis and initiation studies and in place of PMA in the promotion studies. At the end of two years of treatment, there was no substantial evidence for a positive effect in complete carcinogenic, initiator or promotor activity of either diesel particulate suspension or dichloromethane extract in any of the test groups. (no Refs)

86. COMPARISON OF THE MUTAGENIC AND CARCINOGENIC ACTIVITIES OF ASPHALT AND COAL TAR PAINTS USED IN CONTACT WITH POTABLE WATER (MEETING ABSTRACT).

Robinson M, Bull RJ, Cunehil D, Slater R, Meier JR
Health Effects Research Laboratory, US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicologist; 2(1):88 1982

Tanks and pipes used for storage and transport of drinking water are often coated with paints which contain either coal tar or asphalt pitch. We have begun a comparison of the potency of a series of products containing these materials utilizing the Salmonella/microsome assay (Ames test) and mouse skin initiation/promotion studies. Eight enamels were chosen for test; 4 asphalt-based (AP) and 4 coal tar-based (CTP). Initiation/promotion studies were conducted in the SENCAR mouse (40 female per group) utilizing single topical applications. A 20-week promotion schedule was used applying 1 ug of TPA (12-O-tetradecanoyl phorbol-13-acetate) 2 times weekly. Ames test results with AP were negative at up to 10 ul/plate. A very high mutagenic activity was found with CTP with rat liver S-9 fraction. Significant tumor initiating activity was observed with AP as well as CTP. The potency of AP was considerably less, requiring approximately 200 ul/mouse to obtain an average of 0.5 tumors/animal at 20 weeks vs 0.2 ul/mouse required of the CTP. These data correspond to a potency equivalent to approximately 15 to 60 mg of benzo(a)pyrene [B(a)P] per ml of coal tar-based product. Estimates of B(a)P equivalence in AP would be 3 orders of magnitude lower. Total B(a)P and B(c)P content of CTP ranged from 1.9 to 3.4 mg/ml; although total identified polyaromatic hydrocarbon concentrations ranged from 29 to 60 mg/ml. (no Refs)

TESTS FOR MUTAGENICITY, TRANSFORMATION OR CHROMOSOMAL DAMAGE

87. CHOLINE-LIPOTROPE DEFICIENT (CLD) DIET AS A MITOGENIC SUBSTITUTE FOR PARTIAL HEPATECTOMY (PH) IN THE INDUCTION OF RESISTANT HEPATOCYTES BY CARCINOGENS AS A SHORT TERM IN VIVO TEST (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:379 1982

Induction of resistant hepatocytes is a property of many carcinogens useful as an end-point in a short term in vivo test. Cell proliferation is essential for this effect. With non-necrogenic carcinogens, PH has been used as mitogen. CLD diet has been shown to induce liver cell proliferation. Fischer rats were fed CLD diet for one wk, then injected with single or divided doses of 1,2-dimethylhydrazine (DMH) (100 mg/kg), benzo(a)pyrene (B(a)P) (200 mg/kg) or DL-ethionine (E) (50 mg/100 g BW) and the deficient diet continued for an additional week. After a two wk period on a standard basal diet with choline, the animals were assayed for foci of resistant hepatocytes by the Solt-Farber procedure using dietary 2-AAF plus PH with gamma-glutamyl transferase (gamma-GT) as the histochemical marker. B(a)P and DMH each induced 12 foci/cm2 and E 9, as compared to 0-2 with CLD diet alone. Since the CLD diet is associated with hepatocyte proliferation for at least one wk, it now becomes possible to use divided doses or even continuous brief exposure to a possible carcinogen to increase the sensitivity of the assay. The use of the CLD diet facilitates the testing of many possible carcinogens by this procedure. (3 Refs)

88. A METHOD FOR AMPLIFICATION OF SENSITIVITY OF THE C3H 10T 1/2 CELL TRANSFORMATION ASSAY (MEETING ABSTRACT).

Schechtman LM, Kiss E, McCarvill J, Gallagher M, Kouri RE, Lubet RA
Microbiological Associates, Bethesda, MD, 20810
Proc Am Assoc Cancer Res; 23:289 1982

Although the 10T 1/2 cells have been shown to be sensitive to a variety of chemical carcinogens, not all genotoxins can be detected using the standard transformation assay of Heidelberger and coworkers. Assay modifications, eg cell synchronization have been found necessary in certain instances to yield the expected response. In order to enhance its sensitivity we have modified the standard 10T 1/2 ('Level I') assay by a procedure designated 'Level II Amplification,' wherein target cells are replated at various times post-treatment for expression of phenotypic transformation. The technique is applicable both in the absence and presence of metabolic supplements, and does not require cell synchronization. It permits amplification of chemically transformed cells which might otherwise go undetected in the originally treated cell population. This procedure has resulted in detectable transformation of 10T 1/2 cells by chemical classes such as alkylating agents (eg N-methyl-N'-nitro-N-nitrosoguanidine), aromatic amines (eg 2-acetylaminofluorene), nitrosamines (eg diethylnitrosamine), and polycyclic hydrocarbons (eg dibenz(a,h)anthracene), which induce little or no Level I response. Detectable focus transformation is specific for carcinogenic chemicals. No response was observed among untreated cells or those exposed to the non-carcinogens phenanthrene and anthracene, or to solvent vehicles (eg acetone). Moreover, chemicals inducing a Level I response continues to yield a Level II response. (2 Refs)

89. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT-AND INDIRECT-ACTING CARCINOGENS (MEETING ABSTRACT).

Nesnow S, Garland H, Curtis G
Carcinogenesis and Metabolism Branch, US Environmental Protection Agency, Research Triangle Park, NC, 27711
Proc Am Assoc Cancer Res; 23:284 1982

C3H10T1/2CL8 cells are transformed by a variety of structurally different chemicals, including polycyclic aromatic hydrocarbons, aromatic amines, and pyrimidines. It has been reported that C3H10T1/2CL8 cells are insensitive to the transforming effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) unless the cells are synchronized. This finding is particularly interesting because MNNG mutates C3H10T1/2CL8 cells to ouabain resistance without the need for cell synchrony. Aflatoxin B1 (AFB1) also does not transform C3H10T1/2CL8 cells under conditions described by Reznikoff et al. We report here that oncogenic transformation of C3H10T1/2CL8 cells can be improved by treating asynchronous cultures of cells 5 days after seeding. Benzo(a)pyrene-induced transformation was increased fourfold by this method compared with treating the cells 1 day after seeding. MNNG produced an average of 1 focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and AFB1 also produced marked transformation responses when administered 5 days after seeding. However, 4-

dimethylaminoazobenzene and urethane did not induce transformation when administered either 1 day or 2 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. (1 Ref)

90. DETECTION OF CARCINOGENS WHICH INITIATE THE PROCESS OF C3H/10T1/2 CELL TRANSFORMATION (MEETING ABSTRACT).

Boreiko CJ, Abernethy DJ, Frazelle JH
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:285 1982

It is known that Formaldehyde, N-methyl-N'-nitro-N-nitrosoguanidine and aflatoxin B1 initiate the process of C3H/10T1/2 transformation, producing transformed foci only when treated cells are subsequently exposed to the tumor promoter 12 O-tetradecanoylphorbol-13-acetate (TPA). Studies were conducted to establish whether initiation of transformation is a common consequence of exposure to chemical carcinogens. Cell culture conditions optimal for the detection of initiating agents were determined and the ability of carcinogens to transform or initiate transformation examined. Treatment with cytotoxic concentrations of N-nitrosomethylurea, N-nitrosoethylurea, methylmethanesulfonate and ethylmethanesulfonate followed by continuous exposure to 0.25 ug/ml TPA produced foci in at least 25% of the dishes exposed to the highest concentration of each compound. Foci were generally not observed in dishes exposed to TPA alone or in chemically treated dishes not exposed to TPA. Mitomycin C, 5-fluorodeoxyuridine, amethopterin and 5-azacytidine, alone produced foci in 4-47% of treated dishes and exposure to TPA enhanced focus frequency more than two-fold. In the absence of TPA, 3-methylcholanthrene and benzo(a)pyrene produced foci in 50-100% of treated dishes. TPA caused 50% and 22% reductions in focus formation by 3-methylcholanthrene and benzo(a)pyrene respectively. These studies indicate that some classes of carcinogens function as initiating agents in the standard C3H/10T1/2 transformation protocol and that the presence of TPA can significantly enhance the sensitivity of this system to genotoxic substances. (no Refs)

91. MUTAGENICITY OF CARCINOGENS IN CULTURED HUMAN EPITHELIAL CELLS (MEETING ABSTRACT).

Allen-Hoffmann BL, Connell ND, O'Connell T, Rheinwald JG
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Proc Am Assoc Cancer Res; 23:364 1982

Most human cancers arise from epithelial cells. Difficulty in growing these cells has impeded study of the relationship between chemically induced mutation and carcinogenic alterations in human epithelial cells. We used X-rays, N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG), and 7,12-dimethyl benzanthracene (DMBA) to induce mutations in the hypoxanthine-guanine phosphoribosyl transferase locus (HPRT) of human keratinocytes. Mutant cells were selected by resistance to 6-thioguanine (TG). In order to measure mutation in feeder layer-dependent human epithelial cells a TGr clone of the Swiss mouse fibroblast line 3T3 (3T3M1) was isolated. With 3T3M1 it is possible to select HPRT- epithelial cells while fulfilling their feeder layer requirement. Using this modified system we report the first successful selection of mutant human epithelial cells. A near-diploid human squamous cell carcinoma line, SCC-13y, and normal diploid human keratinocytes were used to select for induced mutations. HPRT- keratinocytes from Lesch-Nyhan patients were used to optimize selection conditions for normal human keratinocytes whereas a spontaneous mutant of SCC-13y was used to determine optimal expression time, population density and TG concentration for the carcinoma line. Mutagens increased the incidence of mutants 50-to 70-fold. Mutant colonies from a DMBA-treated population of SCC-13y were aminopterin-sensitive and possessed no HPRT activity. Selection of induced mutants from normal human keratinocytes and mesothelial cells is in progress. (no Refs)

92. INDUCTION OF SISTER-CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES BY EXTRACTS OF PARTICULATE EMISSIONS FROM A DIESEL ENGINE.

Lockard JM, Kaur P, Lee-Stephens C, Sabharwal PS, Pereira MA, McMillan L, Mattox J
(c/o Pereira) Health Effects Res. Lab., United States Environmental Protection Agency, Cincinnati, OH, 45268
Mutat Res; 104(6):355-359 1982

The sister-chromatid exchange (SCE) assay was used to determine the ability of an extract of the organic components of the particulate matter of diesel exhaust to damage human chromosomes. The results were compared to those obtained with benzo(a)pyrene (BaP). The potency of the diesel extract was approx one-fifth that of BaP with a 54-hr exposure time and no exogenous activation. Extract of organic constituents of particles from diesel exhaust is potentially genotoxic to humans. (15 Refs)

93. EFFECTS OF POLYCYCLIC HYDROCARBONS ON THE INDUCTION OF CHROMOSOMAL ABERRATIONS IN ABSENCE OF AN EXOGENOUS METABOLIC ACTIVATION SYSTEM IN CULTURED HAMSTER CELLS.

Kochhar TS
Dept. Biology, Kentucky State Univ., Frankfort, KY, 40601
Experientia; 38(7):845-846 1982

The effect of carcinogenic polycyclic hydrocarbons on the chromosomes of cultured Chinese hamster cells was investigated. Contrary to earlier reports it was observed that benz(a)anthracene, benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene were effective in causing chromosomal aberrations without any exogenous metabolic activation. Duration of incubation with these agents may be the cause of difference in results. Importance of prolonged treatment period is discussed. (Author abstract) (9 Refs)

94. MUTAGENICITY OF BENZO[A]PYRENE AND THE ANTIOXIDANT PHENOL AT THE HGPRT LOCUS OF V79 CHINESE HAMSTER CELLS.

Paschin YV, Ivanitova LM
Inst. Genetics, Acad. Sciences, USSR, Moscow 117809, USSR
Mutat Res; 104(6):389-393 1982

The mutagenicity of benzo(a)pyrene (BP; up to 25 ug/ml) and phenol (PHE; up to 500 ug/ml) towards the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus of V79 Chinese hamster cells was investigated. Both BP and PHE increased the frequency of azaguanine-resistant mutants over the spontaneous level. While PHE alone has no effect on cell survival, BP plus PHE decreased the viability of wild-type V79 cells to 1% after treatment with metabolic activating mixture. (6 Refs)

95. MUTAGENESIS BASED ON DEPURINATION BY CHEMICAL CARCINOGENS (MEETING ABSTRACT).

Loeb LA, Schaaper RM, Kunkel TA
Gottstein Memorial Cancer Research Laboratory, SM-30, University of Washington, Seattle, WA, 98195
Proc Am Assoc Cancer Res; 23:254 1982

An analysis of apurinic sites as an intermediate in mutagenesis by chemical carcinogens has been carried out. Alkylation of the N-3 and N-7 positions on purines in DNA causes cleavage of the bond between the base and sugar yielding apurinic sites. Copying of DNA containing apurinic sites by DNA polymerases in vitro results in enhanced mis-incorporations. Transfection of phix174 DNA containing apurinic sites results in mutagenesis when assayed in Escherichia coli spheroplasts expressing error-prone DNA repair. We measured the infectivity and mutagenicity of phix DNA treated with beta-propiolactone (BPL), benzo(a)pyrene diolepoxide, and N-acetoxy acetylaminofluorene. With each compound, mutagenicity is dependent on the induction of the error-prone pathway. Heating of DNA treated with BPL causes alkaline labile (presumably apurinic) sites and concomitantly an increase in mutagenicity. The reversion frequency of untreated amber 80 DNA is 12 X 10(-6), after treatment with BPL it increases to 25 X 10(-6) and exposure of the BPL treated DNA to elevated temperature results in a further increase to 185 X 10(-6). The increase in mutagenicity is proportional to the number of alkaline labile sites introduced and is in agreement with the mutagenic potential of apurinic sites. These results suggest a model in which bulky adducts terminate DNA replication and induce alterations in the DNA replicating complex. (no Refs)

96. ROLE OF DEPURINATION IN MUTAGENESIS BY CHEMICAL CARCINOGENS

Schaaper RM, Glickman BW, Loeb LA
(c/o Loeb) Joseph Gottstein Memorial Cancer Res. Lab., Univ. Washington, Seattle, WA, 98195
Cancer Res; 42(9):3480-3485 1982

The effect of modifying phichi174 viral DNA by the chemical carcinogens beta-propiolactone, N-acetoxyacetylaminofluorene and anti-benzo[a]pyrene diol-epoxide was investigated by transfecting the modified DNA into Escherichia coli spheroplasts. Modification of the DNA in vitro by each of these agents was mutagenic for the phichi174 amber mutants am3 and am86. Mutagenicity depended on the induction of the 'SOS' response and the host spheroplasts. Heating beta-propiolactone-treated DNA at neutral pH caused strong inactivation such that the number of lethal hits was increased four-fold. Sucrose gradient analysis showed the induction of alkali-labile sites in the heated DNA. The 'nicked circle assay' with double-stranded phichi174 DNA showed greater than 70% of these sites to be apurinic sites. Concomitantly with the production of these new sites, a strong increase in the mutation frequency was observed. This mutagenesis also depended upon the induction of the error-prone SOS response in the spheroplasts, as was previously shown to be the case for mutagenesis at putative apurinic sites induced directly by acid-heat treatment. These results suggest that depurination may be of importance to the mechanism of mutagenesis by beta-propiolactone and other carcinogens. (Author abstract) (25 Refs)

97. MUTAGENICITY OF NITROAROMATIC HYDROCARBONS IN THE SALMONELLA ASSAY: STRUCTURE ACTIVITY RELATIONSHIPS (MEETING ABSTRACT).

Rao TK, Allen BE, Cox JT, Epler JL
Division Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

A selected group of nitroaromatic hydrocarbons was assayed for mutagenicity in the Salmonella histidine reversion assay and several useful conclusions were drawn, based on their chemical structure. Almost all the compounds were direct acting, in that they did not require any addition of exogenous metabolic enzymes (S-9 mix). Strains capable of detecting frameshift mutations (TA98 and TA100) were reverted by these compounds. A dependence on the carbon ring size was noted for mutagenic activity. The larger fused ring structures such as nitroperylene (5-ring) and nitropyrene (4-ring) were more mutagenic than nitronaphthalene (2-ring). Compounds with only one all-carbon ring (nitrobenzene, nitrotoluenes, nitroxylenes) were not mutagenic. However, ring substitution with nitrogen as in nitropyridine, nitrobenzimidazole and nitroquinoline resulted in significant mutagenic activities. Results obtained under aerobic and anaerobic conditions will be compared. The data presented would contribute to a growing information base on chemical structure/mutagenic activity relationships which can lead to a clearer understanding of the mechanism for biological activity. (no Refs)

PHYSICAL, CHEMICAL AND THEORETICAL STUDIES

98. MUTAGENICITY AND K-REGION REACTIVITY OF MONOMETHYL DERIVATIVES OF BENZ(A)ANTHRACENE IN A SELF-CONSISTENT-FIELD MOLECULAR ORBITAL THEORY.

Majumdar R, Mathur SC, Roy R
Dept. Physics, Univ., New Delhi, Delhi 110007, India
Biochem Biophys Res Commun; 106(3):836-841 1982

A self-consistent-field (SCF) molecular orbital (MO) theory was used to examine how the mutagenicity of monomethyl derivatives of benz(a)anthracene (MBA) is related to the corresponding reactivity of the K-region where the addition reactions are likely to occur. The total pi-electron density in the K-region was used as an appropriate index measuring the reactivity of the K-region towards epoxidation. The calculated SCF values of the difference in total pi-electron density in the K-region (deltaQK) were compared with the mutagenicity as demonstrated by the Ames test for the MBA. Hucke molecular orbital (HMO) values are also given. The K-region reactivity as represented by the SCF values of deltaQK for the MBA correlated well with the observed mutagenicity. The only exceptions were the high mutagenicities of 4-MBA and the K-region derivatives, 5-MBA and 6-MBA. Except for the aforementioned compounds, the free valence was always max at the K-region, suggesting that for the exceptions, the K-region reactivity may not be the only controlling factor. The correlation between K-region reactivity and mutagenicity almost disappeared when the HMO values of deltaQK were used instead of the SCF values. The K-region theory, however cannot ac-

count for most of the qualitative data on the corresponding carcinogenic potencies of the MBA. (16 Refs)

99. ISOLATION AND QUANTITATION OF DNA-BOUND BENZO(A)PYRENE METABOLITES: COMPARISON OF HYDROXYAPATITE AND PRECIPITATION PROCEDURES.

Adriaanssens PI, Bixler CJ, Anderson MW
(c/o Anderson) Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Parl, NC. 27709
Anal Biochem; 123(1):162-169 1982

The hydroxyapatite and precipitation procedures are two commonly used methods for isolating DNA, and both have been employed in studies on chemical carcinogenesis. A comparison was made of the specific activity (pmol/mg DNA) of benzo(a)pyrene metabolite-DNA adducts in DNA isolated by the two procedures from the lung, liver, and forestomach of A/HeJ mice given oral benzo(a)pyrene. Total DNA-associated radioactivity per milligram DNA was higher with the precipitation procedure than with the hydroxyapatite method. This was partly due to large amounts of early eluting peaks in the high-pressure liquid chromatography analyses of digests of DNA isolated by the precipitation procedure. However, the specific activities obtained for binding of benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide isomers to DNA isolated by the two methods were in close agreement. The hydroxyapatite procedure resulted in the isolation of purer DNA and required less time and sample handling than the precipitation method. For isolation of DNA from whole tissue for carcinogen-DNA adduct analysis these properties make the hydroxyapatite procedure superior to the precipitation method. Our findings have important implications when comparing the results of DNA-binding studies which employ different DNA isolation procedures. (Author abstract) (23 Refs)

100. SEPARATION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE-DEOXYRIBONUCLEOSIDE ADDUCTS OF SERVACEL DHB (MEETING ABSTRACT).

Dipple A, Costantino N, Sawicki JT
Chemical Carcinogenesis Program, National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:247 1982

Servacel DHB is a m-dihydroxyboryphenylaminoethyl cellulose used as a specific adsorbent for cis diols and we have investigated its potential application to the separation of hydrocarbor-deoxyribonucleoside adducts derived from syn and anti diol epoxides. Adducts derived from anti diol epoxides contain a vicinal cis diol group and should interact with this adsorbent while adducts derived from syn diol-epoxides do not contain a vicinal cis diol and should not be retained. 7,12-Dimethylbenz[a]anthracene (DMBA)-deoxyribonucleoside adducts, obtained by enzymic digestion of DNA from mouse embryo cells exposed to [3H]DMBA, are separated into two fractions on Servacel DHB. From various DMBA-DNA preparations, 40-60% of the adducts have been eluted from the column in pH 9 buffer while the remaining 60-40%, respectively, have been eluted only after the addition of sorbitol to the buffer. The adducts in each of these fractions have been recovered and examined by high pressure liquid chromatography (HPLC). No single adduct detected by HPLC is present in both fractions from the Servacel DHB column, indicating that an effective resolution of adducts is achieved. It is reasonable to conclude that the adducts which bind to the Servacel DHB are derived from an anti diol-epoxide and likely that those that do not bind are derived from a syn diol-epoxide, suggesting that for this potent hydrocarbon carcinogen the syn diol-epoxide may play a major role in DNA binding and in the carcinogenic process. (no Refs)

101. MECHANISMS OF COVALENT BINDING OF BENZO(A)PYRENE DIOL EPOXIDE TO DNA (MEETING ABSTRACT).

Geacintov NE, Hibshoosh H, Ibanez V
Chemistry Department, New York University, New York, NY, 10003
Proc Am Assoc Cancer Res; 23:260 1982

The ultimate carcinogenic metabolite of benzo(a)pyrene, 7beta, 8alpha-dihydroxy-9alpha,10alpha-epoxy-7,8,9,10 tetrahydrobenzo(a)-pyrene (BPDE), binds non-covalently to DNA in aqueous solution within 5ms of mixing (pH 7.0, 5 mM sodium cacodylate buffer, 25 C). This initial non-covalent binding is intercalative in nature and results in (1) acceleration of hydrolysis of BPDE to tetraols, and (2) 5-10% covalent binding. Both the hydrolysis rates and covalent binding were studied as a function of pH and temperature in order to elucidate whether there is an association between these two effects. With increasing pH in the range of 6-10, the hydrolysis rate as well as the kinetics of covalent binding decrease markedly with increasing pH, but the extent of covalent binding remains constant. Similarly, as the temperature is lowered from 25 C to 0 C, the rate of hydrolysis and kinetics of binding decrease with decreasing temperature, but the extent of covalent binding of BPDE to DNA remains constant. It is postulated that the rate determining step for both DNA-catalyzed hydrolysis and covalent binding is the formation of an intermediate carbonium ion derived from non-covalently bound BPDE. (no Refs)

102. IMMOBILIZED ARYL HYDROCARBON HYDROXYLASE FOR DETERMINATION OF BENZO[A]PYRENE IN ENVIRONMENTAL SAMPLES (MEETING ABSTRACT).

Walters SN, D'Silva AP, Fassel VA
Ames Laboratory, Iowa State University, Ames, IA, 50011
Fed Proc; 41(3):1296 1982

Aryl hydrocarbon hydroxylase (AHH) is a major enzyme in the metabolic pathway known to convert benzo[a]pyrene (BaP) and other polynuclear aromatic hydrocarbons to their ultimate carcinogenic form. The amount of BaP present in a sample can be determined by fluorescence measurements of its metabolite, 3-hydroxybenzo[a]pyrene (3-OH BaP) produced by AHH. Immobilization of rat liver microsomal preparations containing AHH confers greater stability and a longer life-time to the enzyme. The immobilized enzyme is less sensitive to changes in pH and temperature than the free enzyme and has altered kinetic properties (decreased Vmax, increased Km). The BaP present in environmental samples containing complex mixtures of carcinogenic and co-carcinogenic compounds has been determined by the immobilized AHH method. This assay method provides a measure of the carcinogenic potential of an environmental sample based on the effects of sample concomitants upon the enzymatic conversion of BaP. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

103. AIR POLLUTION AND CANCER. A REVIEW OF EXPERIMENTAL INVESTIGATIONS.

Madsen ES, Nielsen PA, Pedersen JC
(c/o Nielsen), Stigardsvej 2, DK-2900 Hellerup, Denmark
Ugeskr Laeger; 144(23):1719-1721 1982

A review of studies on the relationship between urban air pollution and cancer shows the presence of mutagenic and/or carcinogenic, mostly organic, compounds (polycyclic aromatic hydrocarbons, polar, directly acting mutagens, eg, substituted derivatives of polycyclic aromatic hydrocarbons and analogous heterocyclic compounds) in urban air. Most of these mutagens and carcinogens are bound to suspended particulates, mostly to respirable particles with small aerodynamic diameter. Surprisingly, high mutagenic activity was found for the compounds extracted from air samples in Copenhagen. (28 Refs) (In DAN)

104. BIOLOGICAL CARCINOGENESIS.

Rich MA, Furmanski F
AMC Cancer Res. Center and Hosp., Lakewood, CO
Biological Carcinogenesis. New York, Marcel Dekker, Inc., 310 pp., 1982.

The general principles which govern carcinogenesis are identified for each of the major classes of carcinogens and the extent these principles are applicable to the carcinogenic process induced by other classes of agents is determined. Current knowledge on the interaction of carcinogens and the identification of biological systems where viral, chemical, and physical carcinogens are demonstrably interactive are described. Mechanisms in viral carcinogenesis are discussed with respect to: T-cell growth, T-cell growth factor, T-cell leukemias and lymphomas and isolation of a new type-C retrovirus, properties of sarcoma growth factors produced by sarcoma virus transformed cells, and interactions of murine leukemia viruses with hematopoietic stem cells. Mechanisms in chemical carcinogenesis are discussed with respect to activation of carcinogenic polycyclic hydrocarbons by metabolism, involvement of a protein kinase in multistage skin tumor promotion, and the effect of tumor-causing chemicals on the control of mutagenesis and differentiation in mammalian cells. Transformation of cloned mammary epithelial cells following combined treatment with mouse mammary tumor virus and dimethylbenz(a)anthracene, virus-cell interactions during hormonal carcinogenesis, and separate pathways for viral and chemical carcinogenesis in the mouse mammary gland are described. A molecular approach to studies of chemical carcinogen-virus interaction is presented. Other presentations deal with multistage recombinational origin of leukemogenic viruses, radiation-induced leukemogenesis, neoplastic transformation of cultured cells by herpes simplex virus type 2 and carcinogens, modulation of adenovirus transformation and replication, and transformation of murine fibroblasts. (682 Refs)

105. CURRENT APPROACHES TO THE EXPERIMENTAL INVESTIGATION OF CHEMICALS IN RELATION TO CANCER OF THE BRAIN.

Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Sellkoff I, Weidelberger C
Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

Chemical induction of brain tumors, current methods for evaluating the carcinogenic potential of chemicals, and possible mechanisms of neuro-oncogenesis are reviewed. Chemical induction of brain tumors by polycyclic aromatic hydrocarbons, nitroso compounds, acrylonitrile, and other chemicals (1-aryl-3,3-dialkyltriazenes, 1,2-diethylhydrazine, azoethane, azoxyethane, and procarbazine) is described. Only a small number of chemicals that induce brain tumors have been identified by routine bioassays of new chemicals. Current guidelines require exposure of a minimum of 50 animals of each sex to 2-3 exposure levels and an equal number of controls. Complete necropsies, diagnosis by an experienced histopathologist, and confirmatory histochemical techniques are essential for properly classified brain tumors. Knowledge of normal variation in tumor incidence between species, strain, and sex is required. A positive bioassay should induce a significantly increased incidence of tumors in a dose-related manner. Possible mechanisms involved in neuro-oncogenesis have been proposed, including the formation and persistance of O6-alkylguanine in brain DNA of rodents and the occurrence of glial cell replication in the presence of promutagenic DNA damage. (48 Refs)

106. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: THE RUBBER INDUSTRY.

IARC Working Group
Div. Environmental Carcinogenesis, International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum 28: 486 pp., 1982.

The carcinogenic risks of exposures to workers in the rubber industry is evaluated. Manufacturing of tires, and other rubber goods are considered with respect to exposures incident to the mixing of elastomers with chemicals and their subsequent conversion into finished products. An historical overview is presented with discussion of the origins of the rubber industry and the developing rubber industry and its occupational health hazards. Manufacturing processes are described for tires, tubes, remolds, and retreads; general rubber goods such as wire and cables, belting, hose, ebonite, rubber footwear, food processing equipment, aircraft deicing equipment, automobile parts; proofed rubber fabrics, adhesives and sealants; and dipped latex products and forms. The chemistry of rubber compounding is reviewed. Exposures in the workplace are discussed with respect to controls, protective equipment, work practices; studies of exposures in the workplace; and biological monitoring. Biological effects include carcinogenic, mutagenic, and teratogenic effects of exposure to accelerators, antioxidants, curing agents; solvents; monomers; talc; carbon blacks; aromatic amines; mineral oils, tar products and polycyclic aromatic hydrocarbons; nitroso compounds; phthalate and adipate esters; and curing fumes and other emissions. Effects in humans other than cancer including dermatologic respiratory, and reproductive, are discussed. Epidemiological studies of carcinogenicity in humans are reviewed: definite associations with cancer of the urinary bladder, lymphatics, stomach, lung, and perhaps, other sites, have been made. (367 Refs)

107. PROBLEMS OF DRUG SAFETY: ARISTOLOCHIC ACID.

Hagemann U, Grase R, Thiele A, Bass R, Schonhofer PS
Institut fur Arzneimittel des Bundesgesundheitsamtes, Stauffenbergstr. 13, D-1000 Berlin 30, W. Germany
MMW; 124(25):611-612 1982

Drugs containing aristolochic acid (AA) or extracts of plants of the genus Aristolochia were banned from the market in West Germany because of uncertainty about drug safety. AA

consists of two compounds, AA-I and AA-II, both of which have as the basic component 3,4-methylenedioxy-1-nitrophenanthrene-1-carbonic acid. Animal studies have indicated that AA is strongly carcinogenic. Problems of determining a 'no-effect' dosage level are discussed. (8 Refs) (In GER)

108. ANTHRACENEDIONE ANTINEOPLASTIC AGENT INHIBITION OF MICROSOMAL DRUG METABOLISM (MEETING ABSTRACT).

Kharasch ED, Cook NI, Novak RF
Department of Pharmacology, Northwestern University Medical and Dental Schools, Chicago, IL, 60611
Fed Proc; 41(3):1573 1982

HAQ, 1,4-bis(2-[(2-hydroxyethyl)amino]-ethylamino)-9,10 anthracene-dione diacetate, has excellent antitumor efficacy but causes significantly less cardiotoxicity than Adriamycin. We showed previously that HAQ inhibited microsomal NADPH oxidation and superoxide formation with little evidence of metabolic activation. Presently, HAQ was found to inhibit N-demethylase and O-dealkylase activities in phenobarbital-induced rabbit liver microsomes and aryl hydrocarbon hydroxylase activity in beta-naphthoflavone-induced microsomes. The inhibition was noncompetitive with respect to substrate concentration with Ki's of 2.6, 2.9 and 3.0 mM respectively, for N,N-dimethylaniline, p-nitroanisole and benzo[a]pyrene. In contrast, HAQ failed to inhibit p-nitroanisole metabolism when the reaction was supported with cumene hydroperoxide. HAQ also inhibited basal and substrate-stimulated microsomal NADPH oxidation. The degrees of inhibition of NADPH oxidation and product formation were comparable. These data, in conjunction with previous studies, suggest that HAQ inhibits electron transfer by microsomal NADPH-cytochrome P-450 reductase, diminishing electron flow to cytochrome P-450. This mechanism differs markedly from that for menadione inhibition of drug metabolism in which accelerated electron flow through P-450 reductase to the quinone diverts reducing equivalents from cytochrome P-450. (no Refs)

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Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
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The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

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